To the Medical Profession

The Sex Hormones

(FOURTH EDITION)

A survey of their
chemical constitution
biological properties
and
clinical applications
with a
classified scheme
of
dosage

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CONTENTS

TREATMENT

ADMINISTRATION

FOREWORD TO THE FOURTH EDITION

THE progress made in the study of the Sex Hormones has resulted in a great increase in their use in clinical medicine, particularly as their effects are now known to extend far beyond their immediate influence on sex functions. In spite of the difficulty inherent in condensing the mass of information available, to bring it within the scope of this Handbook, the text has been further revised and amplified in the light of modern knowledge. The Fourth Edition is therefore presented in the belief that it will be even more interesting and useful than the earlier editions.

CIBA LABORATORIES LIMITED
MEDICAL DEPARTMENT

HISTORICAL

A CHRONOLOGICAL SYNOPSIS OF IMPORTANT DISCOVERIES RELATING TO THE SEX HORMONES

1849 . *Berthold* discovered that the implantation of cock testes caused growth of the atrophic capon-comb.

1911 . *Steinach* successfully prevented castration-changes in females by transplantation of ovaries.

1912 . *Adler* promoted uterine growth with crude extracts of ovary and placenta.

1922 . *Frank* found that liquor folliculi contained an active hormone.

1923 . *Allen and Doisy* announced for the first time a method for the quantitative assay of female hormone preparations—the vaginal smear test.

1927 . *Aschheim and Zondek* discovered that œstrogenic hormone was excreted in the urine of pregnant animals

. *McGee* prepared the first active male hormone extract from the lipoid fraction of bull testes

. *Laqueur, Dingemanse, Hart and de Jongh* discovered œstrogenic activity in male urine.

1929 . *Funk and Harrow* obtained crude active male hormone extracts from male urine.

. *Koch and Gallagher* announced a quantitative physiological test for the assay of male hormone—the capon-comb test.

. *Doisy, Veler and Thayer* for the first time isolated a pure, crystalline sex hormone—œstrone (from pregnancy urine)

. *Butenandt* shortly afterwards independently isolated the same substance and, later, established its structural formula.

1937 . *Deanesly and Parkes* introduced subcutaneous implantation of pellets of steroid hormones, whereby very prolonged action is obtained.

1938 . *Bishop* first applied the technique of pellet implantation for therapeutic purposes.

1938 . *Miescher, Scholz and Tschopp* (Ciba Research Laboratories) described for the first time a series of new esters of œstrone and œstradiol, including œstradiol dipropionate.

. *Miescher and Tschopp* (Ciba Research Laboratories) produced the orally active derivative of testosterone propionate—methyltestosterone.

1938 . *Inhoffen and Hohlweg* first synthesised ethisterone (anhydrohydroxy-progesterone) the orally active derivative of progesterone.

1938 . *Inhoffen and Hohlweg* prepared from œstradiol, ethinyl œstradiol, which is the most potent oral œstrogen.

1940 . *Salmon and Geist* described the buccal (sublingual) method of administering sex hormones.

1944 . *Miescher* (Ciba Research Laboratories) synthesised 7-methyl-bisdehydrodoisynolic acid an orally active synthetic œstrogen closely related chemically to the natural hormone.

CHEMICAL

CLASSIFICATION OF THE SEX HORMONES

Although, as will be shown later, the functions of the sex hormones cannot be sharply differentiated, they may be broadly classified as follows:—

ANDROGENS.

Testosterone and its derivatives. The administration of the members of this series prevents the onset of castration changes in the male—maintaining the secondary sexual characteristics and promoting the development of the accessory sexual organs. Their administration to immature animals brings about precocious sexual development. These functions are described as "androgenic".

ŒSTROGENS.

Œstradiol and its derivatives. They prevent castration atrophy of the secondary sexual organs in females, provoke œstrus, augment motor activity of the uterus and induce premature development of the genital tract in females. These functions are said to be "œstrogenic" It has been suggested (*Parkes*, 1938) that "gynæcogen" would be a more suitable generic term for the members of this group, as they possess actions which are not related to the œstrus cycle, e g. feminisation of the plumage of birds

PROGESTOGENS.

Progesterone is responsible for the characteristic progestational changes of the decidual phase of the menstrual cycle. It reduces the frequency of the uterine contractions, but increases their amplitude and is responsible for the maintenance of pregnancy. Its derivative ethisterone has a similar action

Of the androgens, testosterone, androsterone and *trans*dehydroandrosterone, and of the œstrogens, œstradiol, œstrone, œstriol, equilenin, and equilin have been isolated from animal tissues or excretions. Progesterone and pregnanediol, its inactive excretion product, may also be recovered from the animal organism.

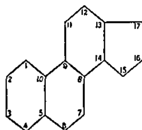
CHEMISTRY AND SYSTEMATIC NOMENCLATURE OF THE SEX HORMONES

The sex hormones furnish a striking example of the differences in biological activity which may be effected by relatively slight alterations in the molecular structure of closely related chemical compounds.

For a proper understanding of these differences and of the apparently paradoxical similarities in the action of male and female hormones, some knowledge of their chemistry is essential.

*CYCLO*PENTANO*PER*HYDROPHENANTHRENE.

All the sex hormones are relatively simple derivatives of a saturated tetracyclic hydrocarbon *cyclo*pentano*per*hydrophenanthrene, which also constitutes the nucleus of the sterols, bile acids, and toad poisons (*Callow and Parkes*, 1937). For convenience in descriptive nomenclature, the position of each carbon atom in the formula is numbered.



*cyclo*pentano*per*hydrophenanthrene

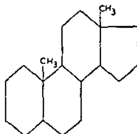
The systematic chemical nomenclature of the sex hormones, although at first sight highly complex, is in reality readily intelligible.

Androgens have the root,*–androst–*, œstrogens,*–œstr–*, and the progesterone group, *–pregn–*.

PARENT SUBSTANCES.

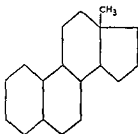
There is a very close relationship between the parent substances, as with their derivatives—the androgens, œstrogens and progestogens.

(a) Androstane



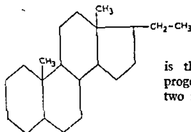
is the parent substance of the androgens and is the dimethyl derivative of *cyclo*pentano*per*hydrophenanthrene.

(b) Œstrane



is the parent substance of the œstrogens and possesses only one methyl group.

(c) Pregnane



is the parent substance of the progesterone group and contains two methyl and one ethyl group.

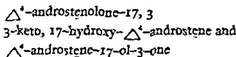
The nature of the derivatives is indicated by a system of prefixes and suffixes.

-ane-	denotes	a saturated compound
-ene-	,,	an unsaturated compound (-triene-denotes 3 unsaturated linkages)
-diol	denotes	a di-hydroxy derivative
-dione	,,	*a di-ketone derivative*
-ol-one	,,	a mixed hydroxyketone derivative
*cis-**	,,	isomeric forms due to a difference in the
*trans-***	,,	configuration of groups round certain carbon atoms especially 3, 5, and 17.
$\triangle^4$ or $\triangle^{4,5}$	,,	the presence and position of an unsaturated linkage (double bond)—in this case connecting the carbon atoms at 4 and 5.

The addition of numerals indicates the position of hydroxyl (-ol) and ketone (-one) groupings. Thus 3, 17-diol denotes the presence of a hydroxyl group at positions 3 and 17, while 17-ol-3-one (or 17, 3-olone) denotes a hydroxyl group at position 17 and a keto group at position 3.

The constitution and nomenclature of the more important of the sex hormone derivatives are given below.

The precise chemical names have not yet attained complete uniformity, in that different writers vary the order of the prefixes and suffixes. A thorough appreciation of the significance, as defined above, of the individual components of these names should serve to prevent confusion. For example, a little thought will show that



$\triangle^4$-androstenolone-17, 3
3-keto, 17-hydroxy-$\triangle^4$-androstene and
$\triangle^4$-androstene-17-ol-3-one

must refer to the same compound.

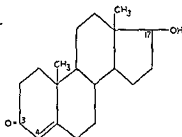
For fuller information concerning steroid nomenclature the reader is referred to *Mason* (1948).

ANDROGENS.

Androgens are derivatives of androstane and a study of their formulæ reveals that the critical points of difference in their constitution are represented by carbon atoms 3 and 17, and the position of the unsaturated linkage.

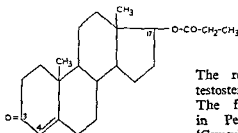
* Also described as "cisoid", "α", and "epi-" forms.
** Also described as "transoid", "β", and "normal" forms.

(a) Testosterone



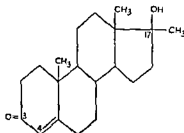
The true hormone of the testis. Δ^4-androstene-17-*trans*-ol-3-one. Obtained from testicular tissue and, artificially, by degradation of the cholesterol molecule. Included in the B.P.C. and used in Perandren Ointment and Implants.

(b) Testosterone Propionate



The result of esterification of testosterone with propionic acid. The form used therapeutically in Perandren Ampoules and 'Crystules'. Included in the B.P.

(c) Methyltestosterone



The methyl derivative of testosterone. This compound is active therapeutically when taken sublingually or orally and is used as the active principle of Perandren 'Linguets'. Included in the B.P.

The nature of the derivatives is indicated by a system of prefixes and suffixes.

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–ene–	„	an unsaturated compound (–triene–denotes 3 unsaturated linkages)
–diol	denotes	a di–hydroxy derivative
–dione	„	a di-ketone derivative
–ol–one	„	a mixed hydroxyketone derivative
cis–*	„	isomeric forms due to a difference in the
trans–**	„	configuration of groups round certain carbon atoms especially 3, 5, and 17.
Δ^4 or $\Delta^{4,5}$	„	the presence and position of an unsaturated linkage (double bond)—in this case connecting the carbon atoms at 4 and 5.

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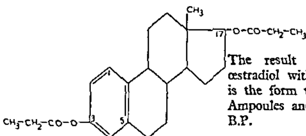
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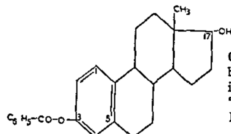
* Also described as "cisoid", "α", and "epi–" forms
** Also described as "transoid", "β", and "normal" forms

(b) Œstradiol Dipropionate



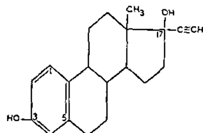
The result of esterification of œstradiol with propionic acid. It is the form used in Ovocyclin P Ampoules and is included in the B.P.

(c) Œstradiol Monobenzoate



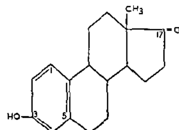
Obtained by esterification with benzoic acid. This form is used in Ovocyclin B Ampoules and 'Crystules'. It is included in the B.P.

(d) Ethinyl Œstradiol



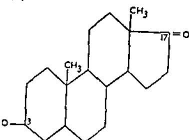
Obtained by replacing hydrogen atom at position 17 with an ethinyl group It is employed therapeutically as Eticyclin 'Linguets'.

(e) Œstrone



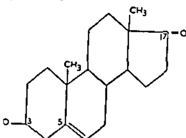
An excretion product of œstradiol, obtained from urine.
$\Delta^{1,3,5}$–œstratriene-3-ol-17-one.

(d) Androsterone



An excretion product of testosterone. Androstane-3-cis-ol-17-one. It is found in male urine and can be obtained by degradation of cholesterol.

(e) Dehydroandrosterone



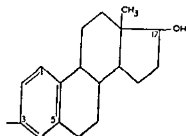
This is probably an intermediary product of the synthesis of testosterone within the body. Δ^5-androstene-3-*trans*-ol-17-one. It can be obtained from male urine or by degradation of cholesterol.

Many other androgens have been artificially prepared in the laboratory. They include androstanediol, androstenediol, androstanedione and androstenedione.

ŒSTROGENS.

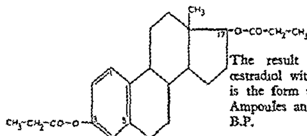
The natural œstrogens are derivatives of œstrane. The term "œstrin" is now obsolete because it does not imply a definite chemical entity.

(a) Œstradiol



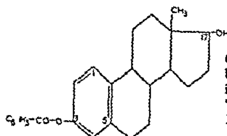
The true "follicular" hormone. $\Delta^{1,3,5}$-œstratriene-3, 17-*trans*-diol. It can be obtained from ovaries or from pregnancy urine. It is employed therapeutically in Ovocyclin 'Linguets', Implants and Ointment and is included in the B.P.C.

(b) Œstradiol Dipropionate



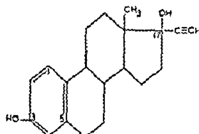
The result of esterification of œstradiol with propionic acid. It is the form used in Ovocyclin P Ampoules and is included in the B.P.

(c) Œstradiol Monobenzoate



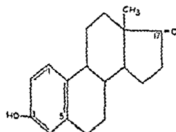
Obtained by esterification with benzoic acid. This form is used in Ovocyclin B Ampoules and 'Crystules'. It is included in the B.P.

(d) Ethinyl Œstradiol



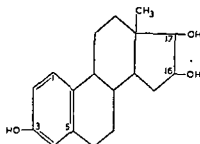
Obtained by replacing hydrogen atom at position 17 with an ethinyl group. It is employed therapeutically as Eticyclin 'Linguets'.

(e) Œstrone



An excretion product of œstradiol, obtained from urine.
$\Delta^{1,3,5}$-œstratriene-3-ol-17-one.

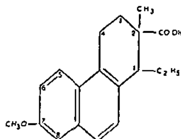
(f) Œstriol



Can be obtained from pregnancy urine and placental tissue.
$\Delta^{1,3,5}$–œstratriene–3, 16, 17–triol.

Among the other known natural œstrogens are equilenin, equilin (both from the urine of pregnant mares), œstrane–3–ol, œstrane–3, 17–diol and œstratriene–3–ol.

(g) 7–methyl–bisdehydro–doisynolic acid

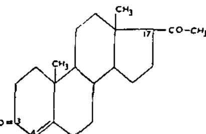


An orally active synthetic œstrogen. Can be obtained from equilenin and is closely related chemically to the natural œstrogens. Known as Fenocyclin.

PROGESTOGENS.

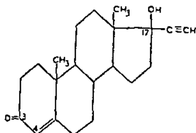
Progesterone was the name decided upon for the corpus luteum hormone by an international group of workers (*Allen, Butenandt, Corner and Slotta*) in 1935.

(a) Progesterone



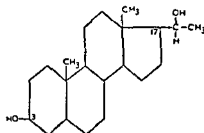
Is sometimes described as pregnenedione. Δ^4 pregnene–3, 20–dione. It can be obtained from the corpus luteum and, artificially, from stigmasterol, a plant sterol found in the soya bean. *It is included in the* B.P. and is employed in Lutocyclin Ampoules, 'Crystules' and Implants.

(b) Ethisterone



Ethisterone, or anhydrohydroxy-progesterone is the progesterone derivative, which is active when administered sublingually or orally. It is in the B.P. and is used in Lutocyclin 'Linguets'.

(c) Pregnanediol



Is found in pregnancy urine and is an inactive excretion product of progesterone.
Pregnane-3, 20-diol.

The B.P. 1948 includes monographs on the following hormones giving physical characteristics, tests for identity and limits of impurities where applicable:—

- Testosterone Propionate
- Methyltestosterone.
- Œstradiol Monobenzoate and Dipropionate.
- Ethisterone.
- Progesterone.

BIOLOGICAL

ESSENTIAL ACTIONS

ANDROGENS.

The essential action of the hormones in this group is the promotion of the growth and the maintenance of the size and function of the accessory sexual organs—the penis, seminal vesicles, and prostate. In the castrated animal these organs undergo atrophic changes which may be reversed by the administration of androgens. In the immature animal the administration of androgens causes premature development of the accessory sexual organs. In addition, the adrenal and thymus glands, which hypertrophy after castration, may be reduced to or towards their normal weight by the administration of androgens The weights of the thyroid, liver, kidneys, and heart, which all suffer post-castration changes, may be restored to normal under the influence of androgenic hormones.

On the basis of the effects produced on the seminal vesicles and prostate, *Korenchevsky and Dennison* (1936) found one "rat unit" of male hormone activity to be present in

8 gamma of testosterone.
21 gamma of androstendiol.
170 gamma of androsterone.
940 gamma of dehydroandrosterone.

In addition to its quantitatively greater activity,

> "testosterone, unlike androsterone, appears to bring about a qualitatively normal development of the male sexual organs, as judged by the ratio of the percentage increase in the weight of the prostate to those of the seminal vesicles and of the penis" (*Korenchevsky, Dennison and Brovsin*, 1936.)

Moore and Price (1938) also found that testosterone propionate acted upon the prostate and seminal vesicles of castrated male rats in the same ratio as the normally secreted testicular hormone

> ". . . . both testosterone and the propionate in effective doses either maintain the normal secretory state of these organs in castrated males of any age, or restore long-

time castrate tissues to the normal secretory state. No qualitative differences have appeared in these tissues conditioned by chemical androgens that would distinguish them from tissues of normal males when proper dosages are employed".

The effects of the ester, testosterone propionate, are much greater than those of testosterone and are maintained for nine days after the last injection (*Korenchevsky, Denniston and Eldridge*, 1937).

In normal adult male rats testosterone and testosterone propionate caused considerable hypertrophy of the accessory sexual organs and hastened the involution of the thymus (*Korenchevsky, Denniston and Hall*, 1937).

ŒSTROGENS.

In castrated female animals the administration of œstrogens causes the development of the accessory sexual organs—uterus, fallopian tubes, and vagina—to normal or supernormal dimensions, and provokes the changes characteristic of the œstrus phase of the sexual cycle. Precocious sexual development may be induced in young animals by the administration of œstrogens. The characteristic effect on the vagina consists of a cornification of the epithelium and the consequent appearance of typical non-nucleated squamous cells in the vaginal smear (see Allen-Doisy test, p. 33).

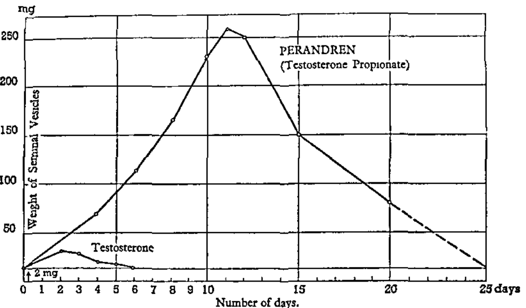
Large doses of œstrogens cause macroscopic enlargement of the uterus with a hypertrophy of all tissue layers, particularly the endometrium. There is a certain parallelism between the duration of the effect on the vaginal smear and on the growth of the uterus (*Miescher, Scholz and Tschopp*, 1938).

Œstrogens also cause rapid growth of the epithelial tissue of the mammary gland (*Allen*, 1938).

PROGESTOGENS.

The action of progestogens may be regarded to a certain extent as antagonistic to that of the œstrogens. As these hormones are concerned, so far as is known, exclusively with the cyclical episodes of menstruation and pregnancy, their actions are considered in the section dealing with those functions.

THE COMPARATIVE ACTIVITY OF ANDROGENS.



Each curve represents the effect of a single injection of 2 mg on the weight of the seminal vesicles of castrated rats.

FIG. 1.

ACTIVATION OF THE SEX HORMONES

David, Dingemanse, Freud and Laqueur (1935), announcing for the first time the isolation of testosterone from the testes, reported that an "X" substance in the testes, itself inactive, had the power of increasing the effectiveness of testosterone.

Miescher, Wettstein and Tschopp (1936), of the *Ciba Research Laboratories*, carried out a detailed investigation of this phenomenon, and found that the same effect could be obtained with a number of fatty acids, including palmitic acid which was found to be present in testis tissue. These findings suggest that the "X" substance is not a specific hormone, but a mixture of the fatty acids naturally occurring in the testis. The same investigators found that even greater effect could be produced by esterification of testosterone. Numerous esters were prepared and tested by their actions on the rat prostate and seminal vesicles and on the capon comb. Of these, the propionate was found to have a particularly favourable effect both in intensity and duration of action, the increase in the weight of the seminal vesicles of the rat following a single injection of testosterone propionate amounting to 12 times that produced by the same amount of free testosterone. These findings with regard to the propionate were fully confirmed by *Parkes* (1936).

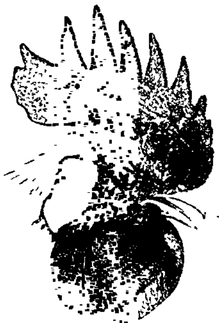
Miescher, Scholz and Tschopp (1938) also prepared and studied the actions of numerous esters of œstrone and œstradiol. Eighteen di-esters of œstradiol, only three of which had previously been described, were investigated, and all of them showed extremely intense and prolonged effects in the œstrus and uterus-growth tests. Of these, œstradiol dipropionate—Ovocyclin P—was selected as the most suitable for clinical purposes. This ester is of special interest, as it displays with a low threshold value a relatively intense and prolonged effect which is proportional to the dose used.

It is perhaps as well to state that esterification of testosterone and œstradiol does not in any way alter their actions qualitatively.

PROMOTION OF COMB GROWTH IN A CAPON BY EXTERNAL APPLICATION OF PERANDREN.



Untreated capon Comb stunted, finely granular, poor blood-supply Wattles shrivelled Surface area, 660 mm-



After daily painting of the comb with Perandren for 2 weeks Comb markedly increased in size, coarse granulations, increased vascularity Wattles fully developed Surface area, 6,500 mm².

FIG. 2.

The pure hormones are absorbed and eliminated too rapidly to exert an intense or sustained effect. *Parkes* (1936) has shown that this wastage may be counteracted to a large extent by administering the same weight of the free hormone in divided doses. Thus, a total dose of 2 mg. of free testosterone administered in 2 injections with a five-day interval causes the weight of the prostate and seminal vesicles of castrated rats to increase from 25 mg. to 54 mg., while the same total dose given in 20 injections at ½-day intervals causes an increase to 272 mg.

However, a much greater increase in efficacy is obtained by esterification than by multiple injections. A single injection of the propionate of testosterone resulted in an increase in the weight of the prostate and seminal vesicles to 343 mg. Summarising these findings, *Parkes* (1936) writes:—

> "It seems therefore that, given as acetate or propionate, the hormone becomes slowly but continuously available to the animal so that the loss by excretion and destruction is very much less than when free hormone alone is administered".

Experiments on the relationship between frequency of injection and effectiveness of testosterone and its acetate and propionate showed (*Parkes*, 1936)

> "(*a*) That even when given in a large volume of oil the free hormone requires to be injected at least once daily to show moderate effectiveness.
>
> (*b*) That provided the total dose is constant, injections of both the propionate and the acetate can be restricted to twice a week without loss of effectiveness and probably even to once a week without serious wastage.
>
> (*c*) That of the two esters, the activity of the propionate is both more intense and more prolonged."

In short, esterification activates the hormones by retarding the rate of absorption and elimination, thus favouring the maximal utilisation of the hormones by the organism.

It was as a result of the most elaborate laboratory investigations of numerous esters of testosterone and œstradiol that PERANDREN and OVOCYCLIN P were introduced by Ciba into clinical medicine. Fuller details regarding this and information concerning the sublingual administration of orally active derivatives, the implantation of pellets and the injection of crystals of steroid hormones are given in the section on Administration. For treatment by inunction, absorption of the free hormones is already sufficiently slow and the esters of testosterone and œstradiol are not therefore used in Perandren and Ovocyclin Ointments.

BIOLOGICAL STANDARDISATION

The availability of the male and female hormones in pure crystalline form renders it unnecessary to assay these substances by biological methods as a means of determining the potency of a given preparation. There are, however, a number of procedures by which hormonal activity can be determined.

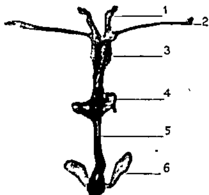
ANDROGENS.

Two methods of standardisation, the Capon Comb and the Seminal Vesicle Tests (*Burn*, 1937), are in use. Each of them depends on the counteraction of castration effects by the administration of the substance to be tested. A third method, the Ejaculation Test, is not commonly employed.

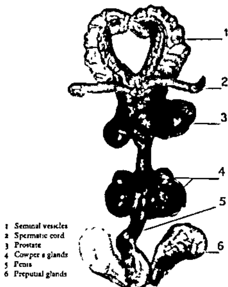
(*a*) The Capon Comb Test. Capons conforming to certain specifications are used. The activity of the sample to be tested is estimated by measurement of the increase in size of the capon's comb which it causes. This increase is compared with that obtained by a known standard. The result is expressed in terms of this known standard, the international unit, and not, as formerly, according to the ability of the sample to cause a certain defined increase in the size of the comb ("Comb-growth unit").

(*b*) The Seminal Vesicle Test. The effect of the sample on the growth of the seminal vesicles and prostate of young castrated rats is compared with that of a known standard.

EFFECT OF PERANDREN ON THE GENITAL ORGANS OF THE RAT.



Genital tract of a castrated rat, showing atrophic condition of the accessory sexual organs



Eleven days after a single injection of 2 mg of Perandren

FIG. 3

(c) The Ejaculation Test. Mice anæsthetised with a barbiturate and injected with yohimbine experience a seminal ejaculation within 5–40 minutes. Castrated mice lose to a large extent this response, which can be restored by previous treatment with androgens. The activity of androgens is compared according to the degree and persistence of restoration of this function achieved by their use.

The comparison of various androgens by the capon comb and seminal vesicle tests does not yield uniform results. Thus different androgens may exert an equivalent effect on comb-growth, but a quantitatively different effect on the rat seminal vesicle.

ŒSTROGENS.

The two commonly employed methods for the assay of œstrogenic activity depend on the power of the sample to counteract castration effects in female rats

(a) The Allen-Doisy Test. (*Vaginal Smear or Œstrus*) In a spayed untreated rat (or mouse), the vaginal smear consists largely of leucocytes with a few nucleated cells and an occasional squamous cell. After injection of an œstrogen the superficial cells of the vaginal epithelium lose their nuclei and form large squamous cells through which leucocytes cannot pass. These changes are characteristic of the œstrus phase of the sexual cycle. In the vaginal smear there is a preponderance of non-nucleated squamous cells and a disappearance or marked diminution of leucocytes. The response obtained with the sample is compared to that obtained with the international standard.

(b) The Uterus-growth Test. Spayed rats receive injections of the sample. After a certain number of days the animals are killed and their uteri weighed. These weights are compared with those obtained by the use of a standard preparation for an equivalent period.

The "rat unit" or "mouse unit", according to the Allen-Doisy method, varies with the criteria adopted by different workers For example, the amount of œstrone in oily solution which represents 1 R.U. has been variously estimated at from 1·0–3·3 gamma, and the amount corresponding to 1 M.U. from 0·125–0·5 gamma.

PROGESTERONE.

(*a*) The Clauberg Test. Injections of progesterone have little or no effect on the uterus of the immature rabbit If, however, the uterus is sensitised by previous injections of œstrogen, progesterone causes typical progestational changes of the endometrium. *Clauberg* elaborated a test on this basis, using immature rabbits which first received ten injections of œstrogen, then a 5-day course of progesterone.

(*b*) The Corner-Allen Test. The *Corner-Allen* test is performed on adult rabbits which are first mated, then castrated. A *Corner-Allen* rabbit unit is the amount of progesterone which, divided into five daily doses, produces by the sixth day a condition of the uterus equal to that on the eighth day of a normal pregnancy.

One international unit (1 mg.) is approximately equivalent to one Corner-Allen unit, two Clauberg units or three "clinical" units.

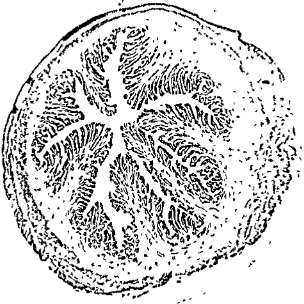
INTERNATIONAL UNITS

An international conference in 1935 laid down certain standards for the comparison of the activity of sex hormones. Since the establishment of these standards, new and more potent male and female hormone preparations (e g. Perandren, Ovocyclin P) have been introduced. For this and other reasons, it is desirable for clinical purposes to regulate the dose of a sex hormone preparation to its content of the pure chemical substance, rather than by any arbitrary units.

(*a*) ANDROGENS. The international standard for male hormone activity is androsterone, which was mainly contributed by *Miescher* of the *Ciba Research Laboratories*, and is stored in the National Institute for Medical Research, London. The international unit of male hormone activity is the "activity of 0·1 mg. of the international standard preparation of androsterone as measured by a specific biological reaction". It was agreed that all comparisons should be made by the capon-comb method.



Uterine horn of a castrated rabbit after daily injections of 50 gamma of œstrone for 7 days The endometrium shows proliferation under the influence of the œstrogen treatment



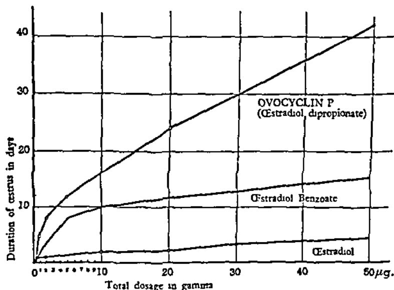
After five daily injections of 0 2 mg of progesterone The endometrium has become transformed to the progestational or secretory phase.

FIG 4

(*b*) ŒSTROGENS. For female hormone activity, two standards have been established—œstrone and œstradiol monobenzoate. The international unit of *œstrone* is defined as the specific œstrus-producing activity of 0·0001 mg. of the standard preparation of œstrone. The international *benzoate* unit is defined as the specific œstrus-producing activity of 0·0001 mg. of œstradiol monobenzoate. The benzoate unit represents a considerably greater activity than the œstrone unit.

(*c*) PROGESTERONE. The international unit of progesterone is defined as the amount of progestational activity present in 1 mg. of the standard substance.

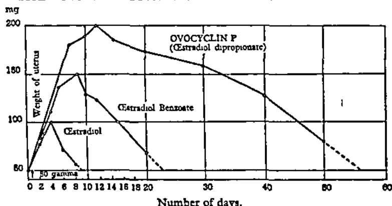
THE EFFECT OF ŒSTRADIOL AND ITS ESTERS IN THE PRODUCTION OF ŒSTRUS.



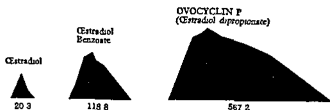
Showing the duration of œstrus produced in castrated rats by different doses of œstradiol, œstradiol benzoate, and Ovocyclin P.

FIG. 5.

THE COMPARATIVE ACTIVITY OF ŒSTROGENS.



The effect of different œstrogens on the uterine weight of castrated rats. The dose of hormone in each case was 50 gamma given in equal parts on two consecutive days.



The activity of different œstrogens as measured on the rat uterus and expressed in centigramme-days. The figures are obtained by planimetric measurement of the area bounded by the curve and the abscissæ (half scale of upper figure)

FIG. 6.

COMPARISON OF THE ACTIVITY OF HORMONES

Figures for the relative activities of the sex hormones are dependent upon the test methods used. As has already been stated, it was agreed by an international commission that the capon comb test should be the standard for comparison of the male hormones.

By this method, testosterone propionate contains 50 international units of male hormone activity (*Miescher, Wettstein and Tschopp*, 1936) in 1 mg. Androsterone, the international standard, contains 10 units in 1 mg. However, when the comparison is made by the seminal vesicle test, testosterone propionate displays an even greater relative activity.

Comparison of the female hormones is rendered complicated by the fact that there are two international units, based upon the œstrus-producing capacity of œstrone and of œstradiol benzoate Furthermore, the comparison of threshold doses does not give an adequate picture of the activity of a hormone preparation.

> "The efficacy of a substance cannot be judged on the results of tests with small doses alone. A proper conclusion regarding the total activity of such a compound can only be made when higher doses are also taken into consideration." (*Miescher, Scholz and Tschopp*, 1938.)

An example should make this point clear. With œstradiol, the threshold dose by the œstrus test in the rat (minimal dose required to produce œstrus in a castrated rat) is 0·4 gamma (0·0004 mg.). The threshold dose of œstradiol dipropionate is 0·75 gamma (in each case administered in equally divided doses as 2 separate injections). As judged by these minimal effective doses, free œstradiol is nearly twice as active as its dipropionate ester. However, when larger doses are employed, a very different relationship is found. Thus, whereas 20 gamma of œstradiol produces an œstrus response for 2–3 days, the

same quantity of the dipropionate ester produces an œstrus of approximately 24 days' duration (see Fig. 5).

Hence,

> "If the compounds tested in this work were judged merely from their threshold values in the œstrus test, then absolutely false conclusions as regards their activity would be obtained". (*Miescher, Scholz and Tschopp*, 1938).

The authors suggest, as a far more satisfactory method of evaluating the effects of the œstrogenic hormones, the plotting of a graph representing the degree and duration of increase in weight of the rat uterus produced by unit doses of each substance tested (Fig. 6). The comparison of activities is made by measurement of the area bounded by the curve and the two abscissæ (one of which represents centigrammes, the other days). Thus the absolute activity of a compound on the growth of the rat uterus may be expressed directly in centigramme-days, or, by adopting the figure for the activity of the free hormone œstradiol as unity, the efficiency coefficient may be expressed in relation to œstradiol.

Example.	GROWTH IN CG-DAYS.	EFFICIENCY COEFFICIENT.
Œstradiol	20 3	1
Œstradiol dipropionate ..	567·2	27·9

In each case the total dose employed was 50 gamma. When œstradiol dipropionate is compared with the other commonly used œstrogenic preparations, the following values are obtained:

Œstrone	0 6
Œstradiol	1·0
Œstradiol benzoate	5·9
Œstradiol dipropionate	27 9

Reference to Fig. 6 shows that the maximum intensity of action is achieved with œstradiol on the 4th day, with the benzoate ester on the 8th day, and with the dipropionate on the 12th day. Both the intensity and the duration of action of the dipropionate are far greater than is the case with free œstradiol. In comparison with the benzoate, œstradiol dipropionate shows a greater maximum intensity and a considerably greater duration of action.

It should be noted that these relationships do not hold good for oral administration, for which purpose esters of œstradiol show no advantage over the free hormone. Estimates of the relative potency of ethinyl œstradiol vary considerably. Comparing it with œstradiol, *Hohlweg and Inhoffen* (1939) found ethinyl œstradiol to be 15 to 20 times more potent than œstradiol when both are given by mouth, *Harding* (1944) 15 to 30 times and *Allen* (1944) about 30 times more potent, whereas *Soule* (1942) concluded that it is 50 to 75 times more active.

As there exists *no international unit for œstradiol* dipropionate, it is of importance for the clinician to have some means of correlating the activity of the dipropionate with the established standards. The international benzoate unit represents the œstrus-producing activity of 0·0001 mg. of œstradiol benzoate, and 1 mg. of the benzoate therefore contains 10,000 international benzoate units of activity.

As the threshold values for œstradiol benzoate and dipropionate are the same, and as the international unit is based upon threshold values, it is permissible to describe 0·0001 mg. of œstradiol dipropionate as 1 "dipropionate unit", which should be roughly equivalent to 1 international benzoate unit. Hence, 1 mg of œstradiol dipropionate may be said to contain 10,000 "dipropionate units".

The results of the uterus-growth test in rats would indicate, however, that the clinical administration of a given number of "dipropionate units" should produce an effect (*a*) of rather greater intensity, and (*b*) of considerably longer duration than an equivalent number of international benzoate units.

AMBIVALENCE OF THE SEX HORMONES

The "male" and "female" sex hormones were at one time regarded as unequivocally masculinising or feminising in their actions. Later investigations have shown, however, that all androgens have some œstrogenic activity and that all œstrogens have some androgenic activity.

> "With few exceptions, bisexual property, though weak in some hormones, must be considered to be one of the common properties of nearly all sex hormones". (*Korenchevsky, Dennison and Hall*, 1937).

That this should be so is not surprising in view of the close chemical relationship of the sex hormones. The ambisexual properties of the sex hormones have been studied in great detail by Korenchevsky and his associates and some of their principal findings are summarised below.

Œstrogenic Effects Produced by Androgens.

(a) **Androstanediol** in large doses caused partial recovery of the atrophied uterus and vagina of spayed rats (*Korenchevsky, Dennison and Simpson*, 1935).

(b) **Androsterone** in large doses caused a return towards normal of the uterus and vagina in spayed rats (*Korenchevsky, Dennison and Hall*, 1937).

(c) **Testosterone Propionate** in spayed rats increased the weight of the uterus nearly to normal and produced an abnormally large vagina (*Korenchevsky, Dennison and Eldridge*, 1937a) Mucification of the vagina and hypertrophy of the uterus, mammæ and nipples were also observed by *Noble* (1939). In normal adult female rats suppression of œstrus, increase in weight of the ovaries and uterus. Increase in the size of the vagina and mucification of the epithelium. Hypertrophy of the mammary glands and nipples (*Korenchevsky, Dennison and Hall*, 1937a). In intact immature mice stimulation of the ovarian follicles, but no formation of luteal tissues (*Starkey and Leathem*, 1938). In immature rats similar follicle stimulation and later production of a corpus luteum (*Salmon*, 1938b). **Testosterone** produces ovulation in amphibia and feminises the plumage of Sebright [illegible]

rabbits (*Klein and Parkes*, 1936). **Methyltestosterone** has greater progesterone-like activity than testosterone in the immature rabbit and is about one-twentieth as active as progesterone. The anomalous activity of male hormone compounds is not due to direct or indirect stimulation of the ovary as it is exerted in the absence of the ovary (*Klein and Parkes*, 1937).

(d) **Transdehydroandrosterone** produced a slight restorative action on the atrophic sexual organs of gonadectomised female rats (*Korenchevsky and Dennison*, 1936).

(e) **Androstenediol** restored the sexual organs of ovariectomised female rats towards normal (*Korenchevsky, Dennison and Eldridge*, 1937a).

Effect of Œstrogens in the Male.

(a) **Œstradiol** caused an increase in the weight of the seminal vesicles and a slight increase in the weight of the prostate. Usually the penis showed no change, although there was a slight increase in some cases (*Korenchevsky and Dennison*, 1937).

(b) **Œstrone** produced the same qualitative results as œstradiol (*Korenchevsky and Dennison*, 1937).

Effect of Progestogens in the Male.

Progesterone.

Korenchevsky and Hall (1937) found no definite effect on male rats, but it has since been shown by *Greene, Burrill and Ivy* (1939) and *Greene, Burrill and Thomson* (1940) that relatively enormous doses of progesterone have an androgenic action in castrated male rats.

CO-OPERATIVE ACTIONS

Certain of the sex hormones show a co-operative action when administered in the form of combined injections. For example, the simultaneous administration of androsterone and œstrone to rats causes a greater increase in the weight of the prostate and seminal vesicles than is caused by androsterone alone (*Korenchevsky, Dennison and Simpson*, 1935). Atrophy of the thymus produced in immature male rats by the administration of œstradiol is intensified by concurrent treatment with testosterone (*Albert*, 1942). The relationships between the sex hormones from the point of view of co-operative activity have been classified by *Korenchevsky and Hall* (1937) in the following manner:—

(*a*) Ambisexual hormones having, in females, no co-operative activity with œstrone or œstradiol.

*Trans*dehydroandrosterone
$\triangle^5$-androstenediol

(*b*) Ambisexual *hormone co-operating with œstrone or* œstradiol to restore the uterus and vagina towards the normal, non-pregnant condition.

Androsterone

(*c*) Ambisexual hormones co-operating with œstrone or œstradiol to restore the size of the uterus and vagina towards normal and the development of changes similar to those seen in pregnancy (progestational type of endometrium and mucification of the vagina).

Testosterone propionate (*in order of relative*
Testosterone *efficacy*)
Androstanedione
$\triangle^4$-androstenedione

(*d*) Purely female hormone co-operating with œstrone or œstradiol to produce changes closely resembling those seen in pregnancy.

Progesterone

(*e*) Combination of hormones which cause normal œstrus. Œstrone and œstradiol do not produce typical œstrus, for the production of which a combination of several hormones would probably be necessary. Such a combination is not, as yet, known.

These findings have important clinical bearings in that they indicate a complex inter-relationship between the sex hormones. It may be that further investigations will yield a basis for the treatment of hormonal deficiencies, not with a single hormone, but with suitable combinations of hormones having a co-operative effect.

ANTAGONISM

While the action of the sex hormones is often co-operative, antagonism may also occur. Large doses of œstrogens suppress the pregnancy changes induced by progesterone (*Korenchevsky*, 1938). *Parkes, Dodds and Noble* (1938) showed that œstrogen

(i.e. ethinyl œstradiol) inhibits the effect of progesterone, prevents the implantation of the blastocyst and interrupts established pregnancy in rabbits.

The œstrogen-induced œdema of the sexual skin in juvenile monkeys may be inhibited by simultaneous injections of progesterone (*Hisaw*, 1938).

When castrated mice are maintained in continuous œstrus by the daily injection of œstrone, the simultaneous administration of testosterone propionate inhibits œstrus (*Spurrel and Ucko*, 1938).

Œstrone and œstradiol inhibit the response of the capon's comb to androsterone; testosterone, methyltestosterone, androstenedione and androstanediol inhibit the response of castrated mice to œstrone (*Emmens and Bradshaw*, 1939).

Œstrone and androsterone cause a smaller increase in weight of the adrenals of the castrated rat than that caused by androsterone alone, although on the accessory sexual organs there is a co-operative action (*Korenchevsky, Dennison and Simpson*, 1935). On the other hand, *Albert* (1942) found that œstradiol caused enlargement of the adrenals of male rats and that this change was inhibited by the simultaneous administration of testosterone.

Testosterone partially suppresses the action of œstrone on the pituitary (*Wolfe and Hamilton*, 1937) and antagonises the cornifying action of œstrone on the vagina (*Callow and Parkes*, 1937). Androgens (e.g. androstanediol, testosterone and especially testosterone propionate) prevent the effects of œstrone on the prostate of laboratory animals (*David, Freud and de Jongh*, 1934; *Zuckerman and Parkes*, 1936; *Zuckerman*, 1936; *Rusch*, 1937).

EXCRETION

The hormone derivatives found in the urine represent excretion products of the primary hormones. Œstradiol is converted in the body to the less active œstrone and œstriol, which are excreted in the urine in two forms, the "free" or "unconjugated" forms and the "conjugated" forms such as œstrone sulphate and œstriol glucuronide (*Cohen and Marrian*, 1936; *Schachter and Marrian*, 1938). Only small amounts of œstradiol have been isolated from urine.

Progesterone is excreted as a completely inactive substance, [illegible]

events of the post-ovulatory phase of the menstrual cycle (see section on "Menstruation").

Testosterone is broken down into and excreted as androsterone, ætiocholanolone (*Callow*, 1939) and isoandrosterone (*Dorfman*, 1941) These are all less active than testosterone, and ætiocholanolone is inactive. They are included in the group of compounds known as neutral 17-ketosteroids, which are thus named because they have a ketone group in position 17 of the *cyclo*pentano*per*hydrophenanthrene or steroid ring.

Since it was first reported by *Laqueur* and his collaborators in 1927 that œstrogens are present in the urine of normal males, it has also been discovered that androgens are excreted in the urine of normal and pregnant females. *Dingemanse, Laqueur and Mühlbock* (1938) estimate the œstrogenic activity of a litre of normal male urine at 70 international units, part of which is due to the presence of œstrone. *Koch* (1937) found marked daily fluctuations in the androgen-œstrogen ratio of the urine of normal men and women. He estimates the average daily excretion of sex hormones as:—

	MEN.	WOMEN.
Androgens	63–68 I.U.	42–56 I.U.
Œstrogens ..	9–12 gamma	18–36 gamma
	(90–120 I.U.)	(180–360 I.U.)

The urine of the stallion possesses a high œstrogen content, its œstrogenic activity being about 400 times that of women's (*Häussler*, 1934), and stallion testis is the richest known tissue source of œstrogens (*Kochakian*, 1937a; *Beall*, 1940). The work of *Tornblom* (1942) suggests that the source of testicular œstrogen is the germinal epithelium.

An interesting observation is that the administration of testosterone propionate to men may increase the excretion of œstrogenic substance in the urine, suggesting that the male organism can convert the male hormone into a substance with female hormone effect (*Steinach and Kun*, 1937). This finding has been confirmed by *Callow, Callow and Emmens* (1939) and by *Dorfman* (1940). The effect can be produced in the absence of the testes.

The ratio of androgen to œstrogen excretion in human urine appears to bear no definite relationship to the possession of those mental and physical attributes generally regarded as "masculine" or "feminine". Some hypogonad males show a super-normal level of androgen excretion, while eunuchs may be well within normal limits in this respect.

The fact that normal amounts of androgens may be excreted by gonadectomised subjects of both sexes (*Parkes*, 1937) proves that the organism is not entirely dependent upon the gonads for the production of sex hormones. It is probable that the normal androgen and œstrogen content of the urine is partly derived from the adrenals (*Parkes*, 1937). Substances with androgenic activity have been isolated from the adrenal cortex, namely, adrenosterone, androstanediolone, Δ^4-androstenedione and "β"-hydroxyprogesterone, and excessive amounts of androgens are excreted in the urine of women with virilising adrenal tumours (*Simpson, de Fremery and Macbeth*, 1936). The 17-ketosteroids, androsterone, dehydroisoandrosterone, isoandrosterone and ætiocholanolone, have been isolated not only from the urine of normal men but also in approximately equal amounts from the urine of normal women (*Callow and Callow*, 1939) and in only a slightly less degree from the urine of castrates of both sexes (*Hirschmann*, 1939; *Callow and Callow*, (1940)). The excretion of the compound dehydroisoandrosterone is greatly increased in patients with adrenal cortical tumours (*Crooke and Callow*, 1939), but it is unaffected by the administration of testosterone propionate. It has been suggested therefore that it is derived from the adrenal glands. The same is probably true of the androgen, 11-hydroxyandrosterone, isolated by *Mason and Kepler* (1945) from the urine of patients with adrenal tumours.

The "male" or "female" hormone is possibly formed by the testes and ovaries respectively from a common parent substance. *Hill* (1937) demonstrated that ovaries grafted into the ears of male castrated mice, in which site they were at a scrotal temperature, exhibited male hormone activity. When the temperature was artificially raised, there was no evidence of male hormone secretion, and a cycle of stimulation and quiescence of masculinising activity could be created by artificial alternations of temperature.

SUMMARY OF ORIGINS AND EXCRETION

The testes secrete androgenic and œstrogenic hormone. The ovaries secrete œstrogenic and androgenic hormone. The adrenals secrete œstrogenic and androgenic hormone. The excretion of androgens and œstrogens in the urine is no guide to the possession of masculine or feminine characteristics.

The excretion of normal amounts of pregnanediol in the urine is strong presumptive evidence of the occurrence of ovulation and the formation of the corpus luteum. Low values or complete absence are of less significance.

ACTIONS

This Section should be read in conjunction with that on Treatment.

MENSTRUATION

THE NORMAL CYCLE.

The menstrual cycle may conveniently be divided into three phases.

(*a*) Œstradiol effect. This is the pre-ovulatory (proliferative or follicular) phase which immediately succeeds the period of menstrual bleeding. The maturing Graafian follicle secretes œstradiol, under the influence of which the endometrium is regenerated. After a short resting stage an extensive proliferation occurs, during which the epithelium becomes of a high cylindrical type and the mucous glands show some convolution and a serous secretion. The occurrence of ovulation marks the termination of this stage.

(*b*) Progesterone effect (predominantly). This is the post-ovulatory (progestational, secretory, decidual or luteal) phase, during which the ruptured Graafian follicle forms a corpus luteum which secretes progesterone and œstradiol. Under the influence of progesterone, the endometrium undergoes a transformation from the proliferative to the secretory or progestational phase. The glands become fuller and richly convoluted, and the glandular cells show an active secretion. By the 7th day after ovulation 3 endometrial zones may be distinguished This transformation is essential for the nidation of the fertilised ovum. Should the ovum not be fertilised, the phase is terminated by the occurrence of menstrual bleeding.

(*c*) Œstradiol-withdrawal effect. This is the bleeding phase. The degeneration of the corpus luteum, and the consequent withdrawal of hormones, results in the breakdown and shedding of the superficial and middle zones of the endometrium, and the menstrual flow. It is well established by many observations that the bleeding is attributable to a withdrawal of œstradiol from the circulation. The administration of œstradiol in high doses to castrate female apes or women causes a uterine bleeding which occurs several days after the last administration—

"withdrawal-bleeding". Smaller doses of œstradiol may cause bleeding during the period of administration—"threshold-bleeding". *Bishop* (1938) found that, in a human female castrate, the threshold bleeding level of œstrone was attained by the injection of 5,000 to 6,000 international units.

Some part must also be played by the withdrawal of progesterone, as the administration of progesterone will inhibit menstruation.

EXPERIMENTAL OBSERVATIONS ON THE PHYSIOLOGY OF MENSTRUATION.

The cyclical endometrial changes have been extensively studied by histological examination of specimens removed from women by curettage at different stages of the cycle and by experimental observations on apes. If fragments of endometrial tissue are transplanted to the anterior chamber of the monkey's eye, the same histological changes are still observed (*Allen*, 1935) thus demonstrating the dependence of these changes upon the circulating hormones. Morphological changes in the endometrium may be correlated with urinary excretion of hormones.

Allen, Diddle, Burford and Elder (1936) studied the excretion of œstrogens during the menstrual cycle of the chimpanzee. This animal undergoes a cyclical swelling of the circum-genital region ("sexual skin") which commences a few days after menstruation, attains a maximum from the 10th to 15th days, is maintained for 10 days, and retrogresses before the onset of the next menstrual flow. Extracts from the sexual skin in its active phase and from its exudate have been shown to possess œstrogenic properties (*Fisher, Krohn and Zuckerman*, 1936). The swelling can also be induced in spayed animals by artificial administration of œstrogens. Assays of the œstrogenic substances excreted in the urine of normal non-pregnant animals showed the greatest yield at the time of maximum swelling, the smallest during menstrual bleeding.

Venning and Browne (1937) succeeded in isolating from urine a reduction product of progesterone—sodium pregnanediol glucuronidate. Estimations during the menstrual cycle revealed that the substance was excreted in the urine only during the

post-ovulatory or luteal phase. In the cases studied, this excretion product of progesterone appeared in the urine within 24-48 hours after ovulation and could be recovered for a period of 3-12 days. Menstrual bleeding occurred within 1-3 days after its disappearance from the urine. The total amount of sodium pregnanediol glucuronidate recovered during an individual cycle varied from 3 to 54 mg.

It has been confirmed (*Hain and Robertson*, 1939) by endometrial biopsies that pregnanediol is not excreted during the proliferative phase, but is found in the urine when the endometrium is in the secretory phase.

SUMMARY OF HORMONAL RELATIONSHIPS DURING MENSTRUATION.

Œstradiol causes regeneration and proliferation of the endometrium, preparing it for the action of progesterone. Progesterone causes a transformation of the endometrium from the proliferative to the progestational type, acting in conjunction with œstradiol to control the endometrial changes of the post-ovulatory phase. Withdrawal of œstradiol and progesterone is followed by degeneration and shedding of the endometrium.

Kaufmann (1933), in what is now a classical clinical experiment, first succeeded in producing true menstruation in a human female castrate by the administration in sequence of an ester of œstradiol and the corpus luteum hormone. The woman was 22 years of age and had had her ovaries surgically removed at the age of 17. Examination of the endometrium before treatment had shown it to be completely atrophic.

ANOMALIES OF THE CYCLE.

(*a*) Anovular menstruation. This type of menstruation is normal among monkeys out of the breeding season and was first observed in them. It occurs occasionally in adult women, frequently in girls at the time of puberty and women at the menopause The Graafian follicle does not rupture, no corpus luteum is formed, and, hence, no progesterone is secreted. The follicle gradually regresses and secretes less œstradiol until the bleeding-threshold is attained. At this point menstruation occurs. It should

"withdrawal-bleeding". Smaller doses of œstradiol may cause bleeding during the period of administration—"threshold-bleeding". *Bishop* (1938) found that, in a human female castrate, the threshold bleeding level of œstrone was attained by the injection of 5,000 to 6,000 international units.

Some part must also be played by the withdrawal of progesterone, as the administration of progesterone will inhibit menstruation.

EXPERIMENTAL OBSERVATIONS
ON THE PHYSIOLOGY OF MENSTRUATION.

The cyclical endometrial changes have been extensively studied by histological examination of specimens removed from women by curettage at different stages of the cycle and by experimental observations on apes. If fragments of endometrial tissue are transplanted to the anterior chamber of the monkey's eye, the same histological changes are still observed (*Allen*, 1935) thus demonstrating the dependence of these changes upon the circulating hormones. Morphological changes in the endometrium may be correlated with urinary excretion of hormones.

Allen, Diddle, Burford and Elder (1936) studied the excretion of œstrogens during the menstrual cycle of the chimpanzee. This animal undergoes a cyclical swelling of the circum-genital region ("sexual skin") which commences a few days after menstruation, attains a maximum from the 10th to 15th days, is maintained for 10 days, and retrogresses before the onset of the next menstrual flow. Extracts from the sexual skin in its active phase and from its exudate have been shown to possess œstrogenic properties (*Fisher, Krohn and Zuckerman*, 1936). The swelling can also be induced in spayed animals by artificial administration of œstrogens. Assays of the œstrogenic substances excreted in the urine of normal non-pregnant animals showed the greatest yield at the time of maximum swelling, the smallest during menstrual bleeding.

Venning and Browne (1937) succeeded in isolating from urine a reduction product of progesterone—sodium pregnanediol glucuronidate. Estimations during the menstrual cycle revealed that the substance was excreted in the urine only during the

is caused by progesterone. These observations are in substantial agreement with those of *Barton and Wiesner* (1945) and *Buxton and Atkinson* (1948).

Halbrecht (1945) suggests that the lowest point of the curve corresponds to the moment of expulsion of the ovum from the follicle. *Greulich* (1946), however, concludes that ovulation occurs with the rise of temperature, for ovaries removed at the low temperature level revealed no evidence of ruptured follicles, whereas in those examined after the temperature had begun to rise there were new corpora lutea. It is possible that luteinization actually begins some hours preceding ovulation (*Davis and Fugo*, 1948).

> "The observation of patients by temperature graphs has proved a valuable aid in diagnosing the effects of hormone treatment on the glands of reproduction. Furthermore, the study of temperature curves aids in deciding on the kind of hormone to be administered and its approximate dosage" (*Nieburgs*, 1945)

The value of this method of checking ovarian function has been confirmed by *Halbrecht* (1945, 1947), who further suggests that it may be particularly helpful in the study of female sterility and in the diagnosis of early pregnancy, delayed menstruation and early abortion.

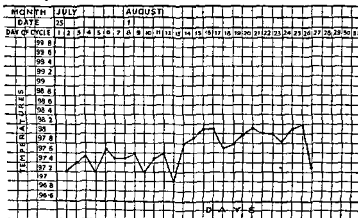


Chart to show ovulation about the thirteenth day of the cycle.
Reproduced by courtesy of "The Family Planning Association."

FIG 7.

be noted that, although progesterone is necessary for a true menstruation (bleeding from a progestational endometrium), it is not necessary for cyclic menstrual bleeding. In anovular menstruation the bleeding occurs from an endometrium which is in the first, or proliferative phase.

(*b*) Metropathia Hæmorrhagica, Glandular Cystic Hyperplasia. Should the unruptured follicle continue to secrete œstradiol in high quantities, a pathological hyperproliferation of the endometrium occurs under its influence. Portions of the hyperproliferated endometrium become detached and are shed, but are regenerated under the influence of a constant œstrogen stimulation. The endometrium may be transformed to the progestational type by artificial administration of progesterone.

OVARIAN FUNCTION AND BASAL BODY TEMPERATURE.

Several investigators have observed a definite pattern of basal body temperature variations through the menstrual cycle. The temperature graph will normally show a constant bi-phasic curve (*Martin*, 1943)—

Pre-menstrual phase	..	fall of temperature
Menstrual phase	..	low temperature
Œstrogenic phase	..	low temperature
Ovulatory phase	..	sudden rise of temperature
Luteal phase	..	sustained elevation of temperature.

Williams (1943) found temperature variations during the cycle to be between 0·9° F. and 1·6° F. with a low point on the day of ovulation, and *Halbrecht* (1945) described an additional slight but constant fall immediately before the luteal phase.

Nieburgs (1945) observed that the administration of hormones had the following general results:—

(*a*) Œstrogens always produce a lowering of temperature.
(*b*) [illegible]
(*c*) [illegible]

The temperature variations correspond to changes in glandular activity and he suggests that a decrease in temperature is an expression of œstrogen activity, whereas a rise of temperature

is caused by progesterone. These observations are in substantial agreement with those of *Barton and Wiesner* (1945) and *Buxton and Atkinson* (1948).

Halbrecht (1945) suggests that the lowest point of the curve corresponds to the moment of expulsion of the ovum from the follicle. *Greulich* (1946), however, concludes that ovulation occurs with the rise of temperature, for ovaries removed at the low temperature level revealed no evidence of ruptured follicles, whereas in those examined after the temperature had begun to rise there were new corpora lutea. It is possible that luteinization actually begins some hours preceding ovulation (*Davis and Fugo*, 1948).

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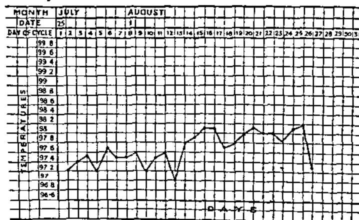


Chart to show ovulation about the thirteenth day of the cycle.

Reproduced by courtesy of "The Family Planning Association."

FIG 7.

The determination of the ovulation date by means of a body temperature graph is a valuable procedure in the treatment of infertility. Conception is more likely to occur if intercourse takes place on or within two days of the ovulation day.

INHIBITION OF MENSTRUATION.

Foss (1937a) reported the successful inhibition of menstruation in a woman by the injection of 50,000 units of œstradiol benzoate at intervals of 3–4 days throughout the cycle. If the injections are delayed until the 19th day of the cycle, 100,000 units should be given, at shorter intervals.

Zuckerman (1937) succeeded in arresting the menstrual cycle in mature rhesus monkeys by bi-weekly injections of testosterone propionate. There was no menstrual bleeding during the period of administration which, in one case, was as long as 7 months. The cycle recurred normally when the medication was discontinued. The monkeys remained in excellent health, and no damage to the internal reproductive organs could be demonstrated by autopsy and histological examination. The only evidence of a masculinising effect was enlargement of the clitoris. The author refers to other experiments in which menstruation was inhibited by anterior pituitary extracts and by progesterone. "It thus appears that, when given in adequate amounts, any of the sex hormones will stop the œstrus cycle".

A clinical application of these observations is proposed.

> "It is suggested that testosterone propionate may be of clinical value for the induction of temporary sterility and the control of uterine bleeding".

The results of *Brown, Bradbury and Jennings* (1948) were somewhat different from these. They found that a single large dose of œstrogen given early in the menstrual cycle (4th, 5th or 6th day) usually delayed, but did not inhibit, ovulation and thereby increased the length of the cycle to 33 to 42 days (average 38 days). Continuous administration of œstrogen in increasing amounts for 30 days throughout the cycle completely inhibited ovulation, but bleeding usually occurred within 3 days after the last dose. Treatment during the luteal phase had no effect on the duration of the luteal phase and did not prolong the length of the cycle. It would appear from these experiments that the most effective method of delaying menstruation is by the

administration of a large dose of œstrogen early in the menstrual cycle. Eticyclin (ethinyl œstradiol) may therefore be given on the first or second day after menstruation in doses of 0.5 mg. four times during the day in order to delay the onset of the subsequent menstrual period.

UTERINE MOTILITY

There is some divergence of opinion concerning the behaviour of the human uterine musculature under the influence of progesterone. In the castrated rabbit it has been shown that the uterus remains in a state of quiescence, that the administration of œstrogen causes a return of uterine motility and that progesterone in adequate amounts counteracts this effect (*Reynolds and Firor*, 1933; *Corner*, 1937). In the same animal *Knaus* (1930) previously concluded that the corpus luteum decreases uterine activity and inhibits the contractions produced by pituitrin It is fairly generally agreed that as far as the rabbit is concerned œstrogens stimulate and progesterone inhibits uterine contractions.

Whether these hormones have the same action on the human uterus there has been some controversy. *Knaus* (1929) studied the problem by inserting in the uterus a small rubber bag filled with sterile water and connected to a mercury manometer with water-filled pressure tubing He found that during the follicular or œstrogenic phase of the menstrual cycle there occurred rhythmic contractions which were increased in amplitude and frequency by the intravenous injection of pituitrin, whereas during the progestational phase the uterus was almost or wholly inactive and failed to respond to pituitrin. He believed that this quiescent state of the uterine muscle was due to the inhibitory effect of progesterone, as in the rabbit. Using a similar method, *Falls, Lackner and Krohn* (1936) found that œstradiol benzoate stimulated, whereas progesterone inhibited the contractions of the human parturient uterus and *Krohn, Lackner and Soskin* (1937) concluded that progesterone decreased the motility of the non-pregnant, non-puerperal uterus. These conclusions have also been reached by other observers.

[illegible]

the latter half of the cycle, increased uterine contractions and

a progressively increasing response to pituitrin. *Moir* (1934), using an intra-uterine bag, observed that the contractions were frequent but of small amplitude during the first half of the cycle and thereafter became less regular but increased in force. *Robertson* (1937) combined these experiments with endometrial biopsies and confirmed their results; he demonstrated a progestational endometrium at the time of greatest uterine activity. *Wilson and Kurzrok* (1938) and *McLellan* (1940) also observed increased uterine contractility during the luteal phase. These results have been amply confirmed by *Henry and Browne* (1943), who studied the question by means of endometrial biopsies, pregnanediol assays and uterine tracings according to *Knaus's* technique. They found two patterns of uterine contractions: one which corresponded to the follicular phase and was characterised by rather small, rapid and fairly regular contractions, and a second, corresponding to the luteal phase, which was distinguished by larger, slower and less regular contractions increasing in amplitude as the luteal phase advanced. The uterus responded to pituitrin throughout the cycle, but its sensitivity was greatest during the luteal phase. An artificially-produced cycle in a castrated woman showed a similar increase in spontaneous activity and response to pituitrin after the injection of 20 mg. of progesterone.

PREGNANCY

When conception occurs, the corpus luteum, instead of degenerating, continues to develop and to secrete œstradiol and progesterone, which in their turn are responsible for the maintenance of the decidual endometrium of pregnancy. Progesterone may also inhibit uterine motility, thus favouring the retention of the uterine contents, but as shown above there is a group of investigators who do not favour this view.

Removal of the ovaries in the early months of pregnancy causes abortion. If, however, the ovaries are removed after the third month, the pregnancy continues to term, as the chorionic villi secrete œstrogen and progesterone. In fact, in the human the corpus luteum remains active only during the earlier months of pregnancy. *Venning and Browne* (1936) believe that the stage of pregnancy at which the placenta takes over the function of the ovaries varies in different individuals and that abortion may in some cases be caused by a hiatus between the production of

progesterone by the corpus luteum and its production by the chorionic villi.

The secretion of progesterone in increasing amounts is continued throughout the whole of pregnancy and suddenly ceases just before parturition. These variations in output are accompanied by variations in the excretion of its degradation product, pregnanediol. *Browne, Henry and Venning* (1937) found that up to the 60th day of pregnancy the urinary output of pregnanediol was 4 to 10 mg. daily and that thereafter there was a gradual rise, the figure on the 150th day being 40 mg. The peak was reached in the 8th month, when figures of 73 mg. and 80 mg. were obtained. Within 24 hours of delivery the excretion of pregnanediol was practically zero. Large quantities of œstradiol are also secreted throughout pregnancy and its excretion products, œstriol and œstrone, may be recovered from pregnancy urine in relatively large quantities. A large part of circulating œstrogen in pregnancy is in the conjugated form which is incapable of sensitising the uterine muscle to the action of pituitrin. The concentration of œstrogen in the blood reaches its maximum at parturition and rapidly decreases after expulsion of the placenta (*Robson*, 1933).

The mechanism responsible for the initiation of labour in the human subject is uncertain. *Robson* (1940) has suggested that the increasing amount of œstradiol and the sudden cessation of secretion of progesterone increase the sensitivity of the uterine muscle to the oxytocic hormone of the posterior pituitary, which causes the characteristic contractions at parturition. However, there is some doubt whether progesterone exerts an inhibitory action on the contractions of the human uterus. *Heckel* (1938) found that the injection of œstradiol benzoate in rabbits during the latter part of pregnancy inhibited parturition and attributed this to the continued activity of the corpus luteum through the influence of œstrogen.

PENILE ERECTION AND MATING BEHAVIOUR

There is little doubt that the administration of male hormone preparations in sufficient doses can stimulate the functions of erection and ejaculation. In fact, the "ejaculation test" is a recognised method for the bio-assay of the male hormone (p. 33).

Hamilton (1937a) found that testosterone propionate had a well-defined action in stimulating erections in immature rodents and monkeys. The erection occurred both spontaneously and as a result of contact with an external object.

In castrated or hypophysectomised rodents the penis decreases in size and erections and copulation occur infrequently. Injection of testosterone propionate maintains the size of the genitals and the frequency of erection and copulation.

The parents of 5 cryptorchid children from 1½ to 11 years old treated by *Hamilton* (1937a) with testosterone propionate commented on the incidence of erections which, in one case, lasted as long as 20 minutes.

A hypogonadal patient of 26, who had only had infrequent erections before treatment, experienced a continual series of erections amounting almost to priapism after treatment with testosterone propionate. Injection with the oily vehicle alone was followed by a sharp decrease in the number of erections, although the patient believed the treatment to be the same.

A married man of 43 who had been impotent for 8 years was given a course of injections of the oily vehicle alone, as a result of which no change in his condition occurred. After a short interval, 20 mg. of testosterone propionate were injected three times weekly. After 3 injections, he reported spontaneous erections while working or sleeping, and, after 6, he was able to achieve successful intercourse twice within a week (*Hamilton*, 1937a). The observations on rodents, monkeys, and cryptorchid children, and the failure of the bland solutions to produce an effect in the 2 cases mentioned above, are sufficient to eliminate any element of suggestion.

In a 30-year old surgical castrate, *Bickel* (1937) was able to induce slight growth of the penis and repeated erections by the administration of testosterone propionate.

Shapiro (1937) found that the injection of testosterone propionate to castrated male rats caused development and hyperæmia of the penis which was followed by mating, whereas before treatment there had been no sexual behaviour.

As the following extracts (*Moore and Price*, 1938) show, the action of testosterone propionate in stimulating mating behaviour in rats is quite unequivocal, even when sexual function has been in abeyance for long periods.

"Testosterone propionate will not only maintain or repair accessory reproductive organs in castrates but its administration results also in the awakening of desire and ability to copulate when castration has been performed before germ cell production."

"Within 2 weeks from the first injection the two treated males exhibited a normal response to females in heat and executed repeated and vigorous copulations with ejaculation, the untreated castrate showed no interest in females".

"*Copulatory ability was developed to its full capacity* within the 3-week period of injections. There is a real copulatory awakening since normal males on the average experience first copulation only about 60 days of age and castration has been performed on day 30".

"The absolute perfection of the copulatory act on the part of males treated with testosterone propionate, and the fact ejaculations occurred, leave no doubt of the entirely normal character of the reaction developed at the end of a castration period of more than 6 months and developed for the first time".

These findings were confirmed by *Sollenberger and Hamilton* (1939), who measured the effects of Perandren on the sexual drive of 15 adult male castrated guinea pigs in terms of:

"(1) the number of times that the animals mounted and (2) the total time spent in copulation with a receptive female within a 10-minute period, (3) the number of times that the animals came in contact with (nudging, licking) and (4) attempted to mount non-receptive females within a 3-minute period".

"By all four criteria the animals injected with this male hormone substance exhibited more activity than animals receiving only the bland vehicle. Upon withdrawal of the hormone the activity of the animal was materially reduced."

Newly hatched chicks, treated for 8 days with testosterone propionate developed cock-like behaviour which included complicated co-ordinated movements such as crowing and strutting (*Hamilton*, 1938a).

Observations by *Miller, Hubert and Hamilton* (see p. 80) confirm that comparable behavioural changes occur in human castrate, hypogonadal, and physically impotent subjects following the administration of Perandren.

Hertz, Meyer and Spielman (1937) found that progesterone proved to be absolutely specific in inducing the copulatory response in female guinea-pigs. Adult virgin animals were castrated and received preliminary sensitising doses of œstrone 2 days before the administration of progesterone. Closely related compounds such as pregnanedione, testosterone, and other sex hormone derivatives were totally inactive in provoking sexual receptivity. The copulatory reflex is suggested as a delicate biological test for detecting the presence of progesterone.

TESTICULAR DESCENT

The successful descent of the testes is to some extent dependent on the development of the scrotum. In castrated or hypophysectomised rats, the scrotum atrophies. If the testes are replaced by "paraffin testes" of equivalent size, weight and shape, the post-castration scrotal atrophy is not prevented.

Subcutaneous injections of testosterone propionate not only prevent post-castration scrotal atrophy, but maintain the characteristic "sexual skin" at the tip of the scrotum and, in immature intact rats, bring about an increase of 1½–2 times in the size of the scrotum (*Hamilton*, 1936).

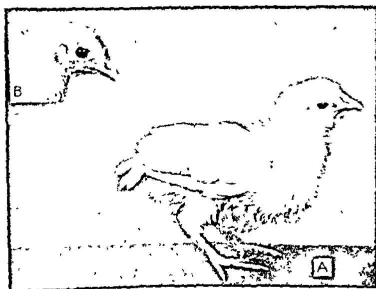
In 9 immature macaque monkeys—normally cryptorchid until puberty—testicular descent was induced within fourteen days by the injection of testosterone propionate (*Hamilton*, 1937b). The descent was apparently attributable to

(*a*) growth and elongation of the spermatic cord, vessels and cremaster.

(*b*) development of the scrotum to receive and retain the testes.

The author suggests the clinical use of testosterone propionate in place of anterior pituitary lobe extracts in the treatment of cryptorchidism.

PRODUCTION OF PRECOCIOUS GROWTH AND DEVELOPMENT OF SEXUAL CHARACTERISTICS BY INJECTION OF PERANDREN.



A White Leghorn Chick, 18 days old. Feathers downy. No comb growth. Weight, 80 grammes.
B Control untreated 38-day chick. Comb growth just beginning. Weight, 150 grammes.



C Same chick as in A, 38 days old, treated from the 20th day by two injections of 5 mg. of Perandren. Complete development of comb and wattles. Feathers transformed. Weight, 312 grammes.

FIG. 8.

In a later paper, *Hamilton* (1938b), referring to the production of premature testicular descent in monkeys, states that there is less œdema and scrotal swelling when testosterone propionate is used than with gonadotrophic substance. He suggests that the descent produced by gonadotrophic substance may be due in part to stimulation of male hormone secretion.

The use of gonadotrophic substance may be preferable to that of the pure androgens in some cases, as the latter, owing to the large dosage used, may produce precocious development, undesirable in boys.

THE PROSTATE

Experimental work on laboratory animals has suggested that prostatic hypertrophy is related to an androgen-œstrogen imbalance, in the direction of a preponderance of œstrogen, due to a failure of testicular function. Immature male rhesus monkeys when treated by injections of œstrone in oily solution show definite pathological prostatic changes. These changes consist of a diminution in the number of true prostatic glands, with an increase in the fibro-muscular stroma and epithelial overgrowth in the region of the uterus masculinus (*Parkes and Zuckerman*, 1935). *Rusch* (1937) obtained similar results in mice by the injection of œstrogens, the prostate undergoing an increase in weight, a metaplasia of the glandular epithelium into a stratified squamous type, and an increase in the fibromuscular stroma He found that the administration of testosterone reversed these changes. *Zuckerman and Parkes* (1936) were able to suppress the prostatic effects of œstrone in monkeys by the injection of androsterone and androstenediol. Progesterone proved inefficacious. A more pronounced inhibition of the œstrone-effect on the prostate of monkeys is obtained by the use of testosterone propionate (*Zuckerman*, 1936), which is able to maintain the normal size and histological appearance of the prostate in doses equivalent to 7 times the amount of œstrone used. The action of testosterone propionate was "still powerful as long as a fortnight after its injection".

In a later study of the effects of sex hormones on the prostate and seminal vesicles of monkeys, *Zuckerman and Sandys* (1939) suggested that testosterone might be of use in the treatment of benign enlargement of the prostate, on the grounds that

not only can male hormone suppress the effects of œstrogenic stimulation, but œstrogens induce growth of that part of the prostate in which fibroadenomata of benign enlargement begin. The effects of male hormone are to reduce relatively the size of that part of the prostate and to stimulate the glandular zone proper, a zone which in benign hypertrophy becomes displaced until it may come to form a false capsule to the much hypertrophied and altered middle lobe.

Sharpey-Schafer and Shackman (1939) failed to find any significant histological change in the hypertrophied prostate of a patient who had received large doses of testosterone propionate, although the prostate was macroscopically reduced to one third of its former size.

THE NASAL MUCOSA

A special relationship appears to exist between the nasal mucosa and sexual function. *Shelesnyak and Rosen* (1938) reported that anæsthetising the nasal mucosa with Nupercaine produced pseudopregnancy in 58 out of 115 female rats. Animals receiving control applications underwent no changes.

Hamilton (1937c), in a series of careful observations upon monkeys, boys and men, found pronounced changes in the nasal mucosa following the injection of testosterone propionate. Macroscopically, there were in all cases a congestion, swelling, and fluid formation In the monkeys, histological examination revealed a congestion with perivascular œdema. *Tebbut* (1938) reported similar changes in the nasal mucosa of both male and female monkeys, the nasal areas affected being those concerned in vicarious menstruation.

Wright and Collip (1936) found that female monkeys showed a cyclical activity of the nasal mucosa which was synchronous with the periodic swelling of the "sexual skin". Artificial administration of œstrogen brought about a similar swelling and congestion. Observations on 60 pregnant women showed a gradually increasing activity of the nasal mucosa, first noticeable at the 3rd month, maximal by the end of the 9th month, and sustained until delivery.

THE SKIN

Pigmentation.

Attention was first drawn to a relationship between skin pigmentation and the sex hormones by *Hamilton and Gilbert* (1938a). They reported that a hypogonad man who had sunbathed in a bathing costume for a short period during the summer, but had failed to acquire a tan, attended some months later for the treatment of his hypogonadism and was given injections of Perandren. During the treatment, the areas which had been exposed to direct sunlight a considerable time before became tanned without any further exposure to the sun. *Hamilton* compares this phenomenon to photographic exposure and development, the Perandren having played the role of a photographic developer. *Hamilton* (1939) has also observed the development of increased pigmentation in five women as a result, in three cases, of the administration of œstrogenic hormone, and in two cases after the administration of Perandren. In one case the influence of exposure to sunshine two months previously was indicated by a white line in the position of the shoulder strap of a sunbathing suit which had been worn by the patient at the time. In another case, the hair was said to have become darker. *Hamblen and Cuyler* (1939) followed up these observations by colorimetric estimations of the androgen excretion of blonde and brunette women and reported that

> "the average daily androgenic titres of true blondes have been found to be distinctly lower than those of marked brunettes".

A practical application of this genito-dermal relationship is suggested by *Lancaster* (1939), who successfully treated with œstrogens several female patients whose skins were abnormally sensitive to sunlight.

Hair-growth.

It is well known that testosterone stimulates the growth of facial, axillary and pubic hair in men and the growth of hair on the arms, chest and legs The injudicious use of high doses of testosterone may also cause hair-growth on the face, chest and extremities in women. Œstrogens, however, do not appear

to be *directly* responsible for the growth of axillary and pubic hair in women. In the rare condition, ovarian agenesis, in which the ovaries are rudimentary, the axillary and pubic hair is still present, though decreased in amount. In panhypopituitarism it is completely absent in these situations. The administration of œstrogen to the patient with ovarian agenesis increases the growth of axillary and pubic hair, but in panhypopituitarism it has no such effect. It has been suggested that the growth of axillary and pubic hair in women is dependent on androgenic hormone produced by the adrenal cortex, which is atrophic in panhypopituitarism but not in ovarian agenesis, and that œstrogen causes growth of hair in ovarian agenesis by stimulating the anterior pituitary which in turn stimulates the secretion of adrenal androgens, a result which cannot be effected in panhypopituitarism because of destruction of the anterior pituitary (*Albright, Smith and Fraser*, 1942). That adrenal androgens may also be responsible for hair-growth in the male is demonstrated by the observation that the eunuch possesses pubic hair of feminine distribution.

The treatment with œstrogens of hirsuties facialis in women would seem to be both irrational and unsuccessful.

CARDIOVASCULAR SYSTEM

Both androgens and œstrogens have been shown to have an important vasodilator effect. Raynaud, in his original description of the disease which bears his name, drew attention to the amelioration of symptoms which sometimes accompanies pregnancy. *McGrath* (1935) showed that œstrogens protect female rats from gangrene induced by ergot. His findings were confirmed by *Suzman, Freed and Prag* (1938) and by *Ratschow and Klostermann* (1938), the former group of workers also showing that castrate male rats are similarly protected. More recently *Burckhardt* (1946) has confirmed the vasodilator effect of œstrogens and androgens.

As a result of these findings, œstrogens and androgens are being adopted clinically in such conditions as angina pectoris, thrombo-angitis obliterans and arteriosclerosis. A summary of the published reports is included in the Treatment section.

After castration typical changes occur in the pituitary, including an increase in the size and number of the basophil cells and an increased production of gonadotrophic substance. The administration of testosterone to castrates causes return of the "castration cells" to normal (*Wolfe and Hamilton*, 1937) and decreased production of gonadotrophic hormone.

The injection of œstrogen into rats and mice increases the weight of the pituitary and causes a complete degranulation of the basophil cells, a partial degranulation of the eosinophils, a marked decrease in the chromophil cells and an increase in the chromophobes (*Wolfe and Chadwick*, 1936; *Wolfe and Hamilton*, 1937). Administration of œstrogen over a prolonged period results in the formation of large hæmorrhagic chromophobe adenomas of the anterior pituitary with evidence of hypopituitarism, e g. atrophy of the testes and ovaries and dwarfism, demonstrating that the hormone depresses pituitary function (*Cramer and Horning*, 1936; *Zondek*, 1936; *McEuen, Selye and Collip*, 1936) There is ample evidence that œstrogen inhibits the gonadotrophic activity of the pituitary (*Rowlands and Sharpey-Schafer*, 1940), but paradoxically it also appears that when given in appropriate dosage it may stimulate the secretion of the pituitary luteinizing hormone and thus produce corpora lutea (*Selye, Collip and Thomson*, 1935).

The injection of testosterone causes no hypertrophy of the pituitary in either sex (*McEuen, Selye and Collip*, 1937; *Wolfe and Hamilton*, 1937). On the other hand, injections of testosterone propionate (*Wolfe and Hamilton*, 1937) and androstanedione (*Nelson*, 1938) counteract the characteristic changes induced in the pituitary by injections of œstrone. Testosterone also has an inhibitory effect on the pituitary *Hamilton and Wolfe* (1938) found that it decreased the gonadotrophic potency of the pituitary of male and female rats It appears that testosterone inhibits the formation of luteinizing hormone (interstitial-cell-stimulating hormone), the production of follicle stimulating hormone remaining practically unchanged (*Laqueur and Fluhmann*, 1942; *Wells*, 1943) *Wells's* experiments were on ground squirrels treated with varying doses of testosterone and testosterone propionate: the interstitial cells of the testes were

severely injured, but the germinal epithelium showed no signs of any change. The failure of testosterone to inhibit the production of follicle-stimulating hormone, except in very large doses, is one of the reasons advanced for postulating the existence of a second testicular hormone, termed "inhibin" (*Klinefelter, Reifenstein and Albright*, 1942; *McCullagh and Hruby*, 1949). Testosterone has been shown to be far less effective in inhibiting pituitary function than œstrogens (*Hertz and Meyer*, 1937; *Meyer and Herz*, 1937).

THE GONADS

It has been shown above how œstrogens when given over a prolonged period cause testicular and ovarian atrophy through inhibiting pituitary function. There is evidence, however, that in smaller dosage they may be concerned in the formation of the corpus luteum by stimulating the secretion of the pituitary luteinizing hormone (*Selye, Collip and Thomson*, 1935; *Ellison and Burch*, 1936).

Reports concerning the effect of androgens on the testis are at variance. It appears to be generally agreed that in hypophysectomized laboratory animals, such as the rat, mouse and rabbit, the administration of androgens will prevent degeneration of the seminiferous tubules and will maintain spermatogenesis (*Walsh, Cuyler and McCullagh*, 1934; *Nelson and Gallagher*, 1936; *Cutuly, McCullagh and Cutuly*, 1937; *Hamilton and Leonard*, 1938). It has been suggested that androgens exert this effect by preventing atrophy of the scrotum (*Cutuly, McCullagh* [illegible]

progesterone also has the property of maintaining spermatogenesis in the absence of the pituitary (*Nelson*, 1936) As there are few cases on record, the production of spermatogenesis in a patient with panhypopituitary hypogonadism by means of testosterone therapy is of interest (*Kinsell*, 1947).

It is in the intact animal where there is a divergence of opinion on the effect of androgens on spermatogenesis. *Korenchevsky, Dennison and Hall* (1937b) subjected adult male rats to daily injections of testosterone propionate over a long period and found a slight depression of testicular development, but no

histological evidence of any injurious effects on the testes "even in the extremely large doses used". *Moore and Price* (1937, 1938), however, observed that high daily doses of androsterone, testosterone or testosterone propionate were less injurious to the testes of rats than "physiological" doses, i.e. doses sufficient to maintain normal growth of the accessory sexual organs in castrated rats, and that the older the animal the less damage was inflicted on the testes with a given dose. In the ground squirrel *Wells and Moore* (1936) found definite stimulation of spermatogenesis as a result of the administration of androsterone and *Wells* (1943) observed no impairment of spermatogenesis with testosterone but severe damage to the interstitial cells. *Goldschmidt and Streber* (1937) found active spermatogenesis in immature rats treated with testosterone propionate, a condition which was not present in untreated control animals.

Other observers have shown that whereas small doses depress, large doses stimulate the testes (*Selye and Friedman*, 1941; *Shay, Gershon-Cohen, Paschkis and Fels*, 1941). Yet others affirm that very small doses stimulate and larger doses depress spermatogenesis (*Rubinstein and Kurland*, 1941). *Greene and Burrill* (1941) have criticized these results and maintain that large doses of androgens neither stimulate nor depress the testes, but maintain them at a normal size. *Zuckerman* (1938) found little change in the testes of monkeys treated with testosterone propionate. *Selye and Friedman* (1941) argue that androgens definitely exert a direct stimulating action on the testes, but that this is not detectable with small doses because their inhibiting effect on the pituitary is greater than their stimulating effect on the testes *McCullagh and Hruby* (1949), however, have concluded that in man testosterone is not a very effective inhibitor of pituitary activity.

Simpson and Evans (1946), as a result of experiments on hypophysectomized rats, have concluded that the stimulation of spermatogenesis by anterior pituitary extracts is due to the action of testosterone produced by stimulation of the interstitial cells by interstitial cell stimulating hormone. Androgens other than testosterone may be concerned. *Nelson and Merckel* (1937) found that the capacity of steroids to maintain spermatogenesis was unrelated to their androgenic activity and that substances, such as androstanedione, of low androgenic potency, were better stimulators of the testicular tubules than testosterone.

severely injured, but the germinal epithelium showed no signs of any change. The failure of testosterone to inhibit the production of follicle-stimulating hormone, except in very large doses, is one of the reasons advanced for postulating the existence of a second testicular hormone, termed "inhibin" (*Klinefelter, Reifenstein and Albright*, 1942; *McCullagh and Hruby*, 1949). Testosterone has been shown to be far less effective in inhibiting pituitary function than œstrogens (*Hertz and Meyer*, 1937; *Meyer and Herz*, 1937).

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[illegible] on [illegible] *De*[illegible] injections of testosterone propionate over a long period and found a slight depression of testicular development, but no

500 gamma of testosterone propionate into rats during the last third of pregnancy. The offspring had no visible vaginal aperture, a large clitoris, scrotum-like perineum, and underdevelopment of the nipples. The internal reproductive system was intact.

Robson (1935, 1937) was able to inhibit the secretion of milk in lactating mice by the administration of comparatively high doses of œstrogen or by the injection of testosterone propionate. These substances inhibit lactation probably by depressing the activity of the anterior pituitary. *Folley* (1936) showed that the administration of œstrogen to lactating cows exerted a protracted galactopoietic effect and later he demonstrated that lactation could be produced in virgin goats by inunction of the udders with œstrogen (*Folley, Watson and Bottomley*, 1941). These effects may possibly be due to activation of the anterior pituitary, for there is evidence that low doses of œstrogen stimulate the gland (*Marrian and Butler*, 1937)

McEuen, Selye and Collip (1937) observed no inhibition of somatic growth in male and female rats after large and long continued injections of testosterone propionate. *Whitney and Burdick* (1936) reported that large doses of œstrogens in mice prevented the descent of the fertilised ovum to the uterus.

Hall and Lewis (1936) injected œstrogens into 6 immature female macaque monkeys over a period of two weeks. The vaginal secretion, which was definitely alkaline before treatment, became highly acid. On withdrawal of the hormone, the pH returned to its previous value.

CARCINOGENIC PROPERTIES OF ŒSTROGENS

It has been shown by *Cramer and Gye* and others that the prolonged administration of œstrogens in high doses is capable of causing mammary cancer in susceptible strains of mice. In view of these observations, and of the known chemical similarity between œstrogens and carcinogens, the question of a possible similar effect of œstrogen therapy in the human subject must arise *Cramer and Gye* (1936), however, have pointed out that the period of administration necessary to produce carcinoma in mice would correspond to 7 or 10 years of the human life cycle. They maintain that

Masson (1945) has also observed that of various steroids tested androstenediol and its derivatives had the most marked spermatogenic activity.

ACTION ON METABOLISM

Thorn and Harrop (1937) discovered that the sex hormones, in common with several steroids of the adrenals, have the property of inducing the retention of sodium, chloride and water. Androgens have been shown to decrease the urinary excretion of calcium, phosphorus, sulphate and potassium and to cause a marked decrease in the urinary nitrogen and creatine (*Kochakian*, 1937; *Kenyon, Sandiford, Bryan, Knowlton and Koch*, 1938; *Knowlton, Kenyon, Sandiford, Lotwin and Fricker*, 1942). These effects are related to the property of androgens of promoting the anabolism of protein. Methyltestosterone, while producing the other effects mentioned, causes an increased excretion of creatine, a discrepancy which has not been satisfactorily explained (*Samuels, Henschel and Keys*, 1942). Recent studies with isotopes (*Hoberman, Sims and Engstrom*, 1948) would indicate that the creatinuria produced by methyltestosterone is due to increased synthesis of creatine rather than tissue breakdown.

Œstradiol also causes nitrogen, calcium and phosphorus retention, but it has to be given in large doses to effect this; it does not alter the excretion of creatine or of potassium (*Knowlton, Kenyon, Sandiford, Lotwin and Fricker*, 1942). It is not yet evident that in physiological amounts œstradiol exerts any definite effect on metabolism. Progesterone, while capable of causing some salt and water retention, has no effect on the other substances mentioned.

So far as is known, the metabolic effects of androgens are exerted directly on tissues without the intervention of other organs of internal secretion (*Kenyon, Knowlton and Sandiford*, 1944). They have the same action on metabolism in the absence of the anterior pituitary or of the adrenals

MISCELLANEOUS OBSERVATIONS

Greene and Burrill (1938) found that the injection of large

TREATMENT

This section should be read in conjunction with that on Actions.

> "The development of mammary cancer described in this paper should not, therefore, be used as an argument against the therapeutic application of œstrin preparations".

Parkes, Bishop and Dodds (1936), dealing with the same question, wrote that

> "It would be a great disservice to practical therapeutics if the use of the sex hormones were to be in any way restricted on account of unsubstantiated speculation".

A writer in the "British Medical Journal" (*Annotation*, 1938), referring to the therapeutic employment of large doses of œstrogens, goes so far as to say that

> "The cancerogenic bogey has been fairly completely laid".

These judgments from such authoritative sources should serve to allay any anxiety as to the possibility of favouring the development of malignant growths by the administration of œstrogens to human subjects. Indeed, it has now been established that œstrogens have a dramatic effect in controlling one form of cancer—that of the prostate. *Huggins* and his collaborators (1941) showed that the administration of œstrogens caused marked improvement in the symptoms of carcinoma of the prostate and their work has since been amply confirmed by investigators both in England and the U.S.A.

PREPARATIONS

The names of the preparations used clinically are given below, together with details of the active principles employed. The reasons for using particular derivatives and fuller information regarding methods of use will be found in the section on Administration.

ANDROGENIC.

Perandren (Testosterone Propionate B.P.):
- Ampoules and vials of oily solution for intramuscular injection.
- 'Crystules' containing the crystalline hormone in *aqueous suspension for intramuscular injection.*

Perandren (Methyltestosterone B.P.).
- 'Linguets' for sublingual administration.

Perandren (Testosterone B.P.C.):
- Implants for subcutaneous implantation.
- Ointment for Inunction

ŒSTROGENIC.

Eticyclin (Ethinyl Œstradiol):
- 'Linguets' for sublingual administration.
- Scored tablets for oral administration.

Ovocyclin B (Œstradiol Monobenzoate B P.)
- Ampoules of oily solution for intramuscular injection.
- 'Crystules' containing the crystalline hormone in aqueous suspension for intramuscular injection.

Ovocyclin P (Œstradiol Dipropionate B P).
- Ampoules of oily solution for intramuscular injection.

Ovocyclin (Œstradiol B.P.C):
- 'Linguets' for sublingual administration.
- Implants for subcutaneous implantation.
- Ointment for inunction.

PROGESTOGENIC.

Lutocyclin (Progesterone B.P.):
- Ampoules and vials of oily solution for intramuscular injection.
- 'Crystules' containing the crystalline hormone in aqueous suspension.
- Implants for subcutaneous implantation

Lutocyclin (Ethisterone B P.):
- 'Linguets' for sublingual administration.

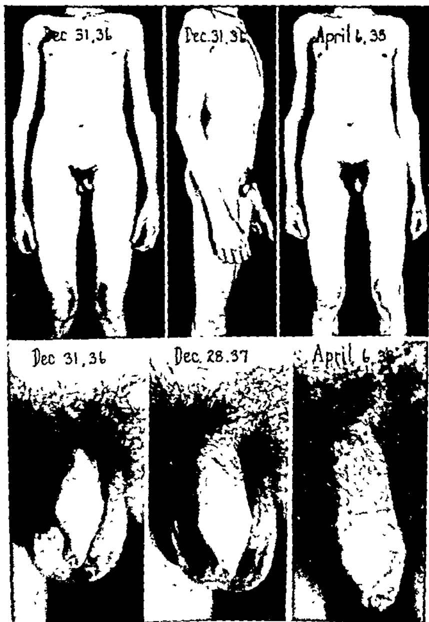


FIG 9.

Hypogonadal patient, aged 22, treated by twice-weekly injections of testosterone propionate for a period of 6 months. The treatment

SEX HORMONES IN THE MALE

HYPOGONADISM, EUNUCHOIDISM, EUNUCHISM.

Where there is evidence of deficient testicular function, the administration of Perandren brings about the development of the secondary sexual characteristics to, or towards, normal. A 27-year old "physiological castrate" who had not responded to previous treatment with an anterior pituitary extract showed marked improvement under the influence of Perandren (*Hamilton*, 1937d). The infantile external genitalia increased in size, there was a growth of hair on the chest and in the pubic region, and there was a marked elevation of spirits and of the capacity for work.

Villaret, Justin-Besançon and Rubens-Duval (1938) treated a 21-year old eunuchoid by daily injections of 10–30 mg. of testosterone propionate. After one month there was a marked development of the external genitals. Later, the voice broke, the face assumed a more manly appearance, there was a growth of hair, and an increase in height, weight and muscular development. The testicles grew to three times their former dimensions, but, even then, did not correspond in size to the age of the patient. After 6 months, the last trace of infantilism had disappeared. *Bickel* (1937) was able to promote the development of secondary sexual characteristics in a 30-year old surgical castrate.

Perhaps the most striking results of the use of Perandren in this field were obtained by *Vest and Howard* (1938). In one hypogonadal patient the infantile penis was increased in length from 2 cm. to 10 cm. and this growth was associated with proportionate changes in the other accessory sexual organs and in the secondary sexual characteristics. At the same time there was a pronounced psychological improvement. No case failed to give satisfactory response The conclusions drawn from this study were:—

> "The use of testosterone propionate in 6 cases of hypogonadism and 2 cases of prepubertal boys is reported. It seems to be a satisfactory replacement therapy for hypogonadism in the human We have shown it pro-

duces profound anatomical changes resulting in the proportionate growth of the phallus, scrotum, seminal vesicles and prostate, as well as development of pubic, axillary and extremity hair. There have been laryngeal changes, the appearance of considerable prostatic secretion, and an ejaculum with coitus, and marked changes in the skin. There have been, in addition, changes in the general appearance, with improvement in the personality content. It has induced libido and potentia in individuals in whom these had not existed previously, and restored normal sex life in a patient who was impotent following castration. No evidence of increase in tolerance to the drug has been noted."

In a later paper, *Kenyon* (1938) reported similar results in 4 eunuchoid patients treated by testosterone propionate.

"There was in all patients an early increase in erections, in 3 an enlargement of the penis, in all an enlargement of the prostate, in 2 a distinct deepening of the voice, in 3 an increase in sexual hair".

While *Vest and Howard* found that the testicles of some of their patients became slightly enlarged, *Kenyon* was unable to detect any change in testicular dimensions.

Webster (1938) successfully treated with Perandren six cases of adolescent hypogonadism, and concluded:—

"It would seem that this substance offers a means of inducing in hypogonadal adolescent males, the anatomical changes which occur normally at puberty."

In a further series of 6 cases of hypogonadism (*McCullagh*, 1939), substantially similar results were recorded

The effects of androgen treatment in male hypogonadism have been confirmed by a large number of observers (*Foss*, 1937b, 1939; *Rubinstein*, 1938; *Turner*, 1939; *Spence*, 1940a; *Eidelsberg and Ornstein*, 1940; *Escamilla and Lisser*, 1941, *Joel*, 1942; *Pullen, Wilson, Hamblen and Cuyler*, 1942; *Lisser and Curtis*, 1943, *Heller and Nelson*, 1948).

Dosage: See p. 141.

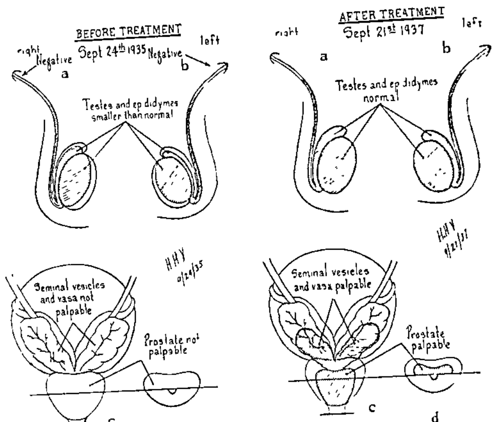


Diagram showing the changes recorded in the prostate, seminal vesicles, and testes after treatment with testosterone propionate

Vest and Howard (1938)

FIG. 10

CRYPTORCHIDISM.

In the case of the "physiological castrate" quoted above, both testes were impalpable. After 2 weeks of Perandren treatment, the scrotum became larger, rugose, more pendulous, and pigmented. After another week, both testes and epididymes were palpable in the scrotum. In immature monkeys, testosterone propionate brings about premature descent of the testicles (p. 62). *Blériot* (1938) treated 9 cryptorchid boys by injections of 5–10 mg. of Perandren twice weekly. Descent of the testes was usually observed after a total of 100–150 mg. In some cases, complete descent was not attained. *Grignon* (1938) induced testicular descent and enlargement of the external genitals in a cryptorchid boy of 13, after 15 injections of Perandren. *Harding* (1943) combined testosterone with gonadotrophins in the treatment of 47 patients with cryptorchidism and obtained successful results in 76 per cent. In cases in which there exists a mechanical obstacle to the complete descent of the testes, no form of hormone therapy can be successful. However, preliminary treatment with Perandren should constitute a very valuable adjunct to operation, as it brings about changes in the scrotum and testicular appendages (p. 62) which must favour retention of the testes in their normal position.

Hamilton (1938b) believes that male hormone preparations may be of value in:—

(*a*) Producing testicular descent in certain cryptorchid cases.

(*b*) Discriminating, at an early age, between those cases where there is no mechanical obstruction to descent and those in which operation is necessary. In this way the injurious effects of late retention may be avoided.

(*c*) Supplementing surgical measures, pre-operatively by the development of cord structures, and post-operatively by preventing retraction and tension

It is often claimed that testes which can be made to descend by hormone therapy will descend of their own accord at puberty. Of many cases this is certainly true, but not of all. *Greene* (1941) says—

> *"This appears to be true of the majority. Yet the hidden testicle is subject to ills which make its treatment by some means necessary. Malignant degeneration may occur and the risk is probably not reduced by operation. Atrophy*

is a real danger, but happily it does not occur until puberty. Unless there is associated hernia, patients should be left untreated until puberty, when treatment will often be unnecessary. At the first signs of puberty, a course of 3 months endocrine treatment should be given. This will induce descent in a few more patients. In the others, it will enlarge the testicles and improve the blood supply, thus rendering easier the surgeon's task. Operation must never be delayed for more than a year."

Dosage: See p. 141.

IMPOTENCE.

Although impotence is due to various causes, consisting mainly of psychological and endocrine disturbances, it is recognised that psychological factors account for the majority of cases. The endocrine causes include not only eunuchism, eunuchoidism and hypopituitarism, but also diabetes mellitus, acromegaly, Cushing's syndrome, thyroid disease and adrenal disease. It may also occur as a result of declining testicular function in old age. It is in these endocrine cases that Perandren has been shown beyond any reasonable doubt to be capable of increasing libido and provoking penile erection.

The observations of *Hamilton* and others on hypogonadal rodents, monkeys, boys and men demonstrate that testosterone propionate is capable of provoking penile erection in the total absence of any element of suggestion. *Foss* (1937b) reported very striking results in a post-pubertal eunuch who had been quite impotent for 19 years and had never been able to consummate his marriage. Treatment with testosterone propionate in 20 mg. doses was given for a dermatitis, the patient being unaware of the possibility of an effect on sexual function. After seven daily doses, the patient requested that the treatment should be postponed, as a persistent priapism was disturbing his sleep. Coitus had been carried out nightly since treatment was begun. The injections were given less frequently and it was ultimately found that a dose of 40 mg. of testosterone propionate weekly was sufficient to maintain full sexual power.

In cases of testicular deficiency the effect of derivatives of testosterone in restoring sexual function has been amply confirmed, as has been shown in the section on Hypogonadism. Many writers have commented on the improvement in affective

sex hormones in the treatment of the condition is, in the hands of most observers, not entirely satisfactory. Testosterone propionate is ineffective, but there are reports that œstrogens are occasionally efficacious, so long as the condition is not associated with poor erections (*Heckel*, 1944). Only small doses should be given, e.g. Eticyclin 0·01 mg. once or twice daily.

Dosage: See p. 142.

STERILITY.

A discussion of all the various ætiological factors in human sterility is beyond the scope of this book: the only aspect of the problem that is relevant here is faulty spermatogenesis, resulting in azoospermia or oligozoospermia. A brief account of the conflicting results obtained with testosterone on the testes of laboratory animals has been given on page 68. The results in patients with faulty spermatogenesis are as conflicting. The difficulties with which the investigator is faced in tackling the problem in man are, (1) accurate observations are more difficult to make on the human than on experimental animals, and (2) whereas the experimental animals used were either normal or were subjected to the straightforward operation of hypophysectomy, the spermatogenic tubules of the human patient are pathological and may be so degenerate as to be beyond repair. In the human subject a useful procedure before the initiation of hormone therapy is a testicular biopsy, whereby the condition of the germinal epithelium may be studied.

It seems to have been fairly definitely established that the doses of testosterone propionate required for the treatment of eunuchoidism have a depressing effect on spermatogenesis. (This effect need not be taken into account in treating a eunuchoid patient, as his seminiferous tubules are completely degenerate, the aim of treatment being to restore his potency and his secondary sexual characteristics). *Rubinstein and Kurland* (1939), *McCullagh and McGurl* (1940), *Heckel* (1940) and *Hotchkiss* (1944) have all observed *suppression of spermatogenesis with* doses of testosterone propionate varying from 10–50 mg. daily to 25 mg. three times a week. The question whether such

tone and mental activity which has resulted from the administration of testosterone.

Miller, Hubert and Hamilton (1938) studied the mental and behavioural changes in six patients who had been treated with Perandren. Of these, two were castrates, two hypogonadal and two were suffering from functional impotence. Before treatment all patients were lacking in conscious sexual desire, erectile capacity or the ability to derive any sexual pleasure from minor forms of amorous behaviour. All patients suffered from symptoms of anxiety or depression. After treatment there was a marked improvement in each case, with a return of sexual power, disappearance of depression and enhanced physical and intellectual energy. It is noteworthy that before treatment with Perandren, control injections had failed to bring about these changes.

In **psychogenic or functional impotence,** however, there is no evidence that a deficiency of androgens exists and as testosterone is not an aphrodisiac it can hardly be expected that Perandren will produce any noteworthy benefit. On the other hand, its administration may create that confidence necessary for combating a psychological inhibition The most striking results in the treatment of impotence with Perandren were obtained by *Huhner* (1939) in seven cases. The author comments:—

> "My results are the more remarkable because I tried it (Perandren) out only in the most obstinate forms of impotence, cases which had resisted all treatment, including operations, for a period of years."

Although *Huhner's* results have not been confirmed by other observers (*Rennie, Vest and Howard*, 1939; *Spence*, 1940b; *Creevy and Rea*, 1940; *Heckel*, 1944), it is a wise therapeutic procedure to initiate treatment of functional impotence with Perandren and combine it with those methods of psychological therapy which may be necessary.

Dosage: See pp. 141, 142.

PREMATURE EJACULATION.

Premature ejaculation may be due to irritation as a result of local inflammation or, more commonly, to psychological factors, when it may be related to psychogenic impotence. The use of

testosterone affects adversely the seminiferous tubules of the testes and the process of spermatogenesis. *Kinsell* recently dealt a severe blow to this structure when he reported spermatogenesis resulting in a "panhypopituitary" eunuchoid man from the administration of testosterone following a supposedly proven, non-effective course of gonadotrophins".

Dosage: See p 142.

CHRONIC HÆMOSPERMIA.

The occurrence of blood in the semen may be due to a variety of causes, the commonest, according to *Parker* (1942), being sexual excess and tuberculous seminal vesiculitis. *Huggins and McDonald* (1945) have described seven cases of unknown ætiology, which had successive blood-stained ejaculates over long periods of time. As a result of their investigations they concluded that the site of the hæmorrhage was in the seminal vesicles. Six patients they treated with ethinyl œstradiol in doses of 0 05 mg. varying from three times weekly to twice daily depending on the response obtained. Four patients had complete remissions; in one the duration of treatment was too brief and another was refractory to the oral administration of œstrogen. During treatment the volume of semen was greatly reduced, but on discontinuing treatment it returned to normal, with the important difference that in the successful cases blood was absent. The rationale of œstrogen therapy lies in the fact that œstrogens in relatively small doses depress or eliminate the secretions of the seminal vesicles.

Dosage: See p. 142.

THE MALE CLIMACTERIC.

[illegible]

in both sexes. The symptoms may be classified as (*a*) neuro- [illegible]

[illegible]

As *Werner* has pointed out, probably a greater number of men than women pass through the climacteric without evident

the administration of a total of 10,000 mg. of testosterone propionate given in four courses over a period of ten months.

Rubinstein and Kurland (1939) have studied the effect of small doses of Perandren on spermatogenesis and used as their subjects 8 normally constituted adult males. They found that Perandren administered

> "in 5 mg. intramuscular doses 3 times weekly led to an increase in spermatozoal counts. This increase was maintained throughout the duration of treatment in all but one case, in which in spite of treatment the elevated count receded to normal after several weeks. Increasing dosage to 25 mg. per injection in the normal adult led to a suppression of the spermatozoal output. Whether counts were elevated or depressed during treatment, cessation of therapy led, either promptly or after several weeks, to the return to normal figures. The oligospermic individual required more hormone to raise his count than did the normal".

> "A childless patient displaying 50 per cent. hypomotile sperm responded with an increase in motility. His wife became pregnant after two months of treatment".

Kinsell (1947) has reported the favourable effect of testosterone on spermatogenesis in a "panhypopituitary" eunuchoid patient, whose external genitalia were infantile and secondary sexual characteristics absent. Treatment with equine gonadotrophin was without effect. After cessation of all therapy for one month he was treated with methyltestosterone for 18 days; this was followed by the implantation of 250 mg. of testosterone and of a further 300 mg 3 months later and again 2 months later. Whereas before treatment with testosterone no mature spermatozoa were found in his ejaculate, one month after the last implantation it contained 18,000,000 mature spermatozoa per cubic centimetre.

Perlman (1949), who observed spermatogenesis in a patient with eunuchoidism following treatment with methyltestosterone and gonadotrophin, writes:

> "A flimsy structure, based principally on data derived from a small number of inconclusive animal experiments and inconsistent clinical experiences with humans, has been erected to support the unwarranted contention that

testosterone affects adversely the seminiferous tubules of the testes and the process of spermatogenesis. *Kinsell* recently dealt a severe blow to this structure when he reported spermatogenesis resulting in a "panhypopituitary" eunuchoid man from the administration of testosterone following a supposedly proven, non-effective course of gonadotrophins".

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Dosage: See p. 142.

THE MALE CLIMACTERIC.

[illegible]

in both sexes. The symptoms may be classified as (*a*) neuro-circulatory, (*b*) psychosexual, (*c*) genito-urinary and (*d*) [illegible]

As *Werner* has pointed out, probably a greater number of men than women pass through the climacteric without evident

disturbance and, because of the belief that men do not have a climacteric period, the condition has probably been overlooked or ignored in men. *Goldman and Markham* (1942) comment:

> "Although we cannot use impotence or the symptoms of prostatism or neuro-circulatory disturbances individually as criteria for establishing the definite presence of endocrine imbalance, the related presence of all or some of these symptoms in a patient is indicative that we may be dealing with the male climacteric".

Schmitz (1937) administered Perandren to 42 patients with symptoms attributable to the male climacteric and including depression, nervousness, impotence and early prostatic symptoms. In 36 patients a pronounced improvement was obtained. *Klein* (1938) has reported a similar success in a patient of 54 years.

Werner (1939) described two patients in the climacteric, both of whom had tachycardia, dyspnœa, palpitations and flushes and were completely relieved with Perandren. *Thomas and Hill* (1940) obtained remarkable improvement in two patients with involutional melancholia treated with testosterone propionate. *Goldman and Markham* (1942) have reported 7 patients suffering from an effort syndrome, together with weakness, muscular aches and pains, irritability, depression and restlessness; 6 responded favourably to testosterone propionate. Similarly satisfactory results were obtained by *Heller and Meyers* (1944) in 20 patients treated with testosterone propionate. All showed improvement and relapsed when placebos were substituted.

Simonson, Kearns and Enzer (1944), in a well-controlled experiment, examined the effects of methyltestosterone on the fusion frequency of flicker and back-muscle strength of 6 men, aged 48 to 67 years, complaining of fatiguability, and observed *significant improvement* in their performance. They concluded that the maintenance of a higher level of male sex hormones has an influence on the depression of working capacity with age.

From these results the use of Perandren in the treatment of premature senility and the male climacteric would appear to be justified.

Dosage: See p. 142.

BENIGN PROSTATIC HYPERTROPHY.

The theoretical basis of the treatment of prostatic hypertrophy with Perandren has been discussed on page 63. As a result of this experimental work a large number of papers have appeared, in some of which it is maintained that testosterone is of benefit in this condition, in others that these experiments were ill-controlled and that there is no scientific evidence that the hormone is of permanent value. *Greene and Robson* (1948), discussing the problem, write:

> "Although controlled experiments have disposed of the hope that androgenic treatment would offer a cure for enlargement of the prostate, the excellent results of treatment in occasional patients cannot be gainsaid".

Whereas *Heckel* (1940) found little improvement in the symptoms and clinical course of 22 patients treated with testosterone propionate and no histological differences in the prostate of those treated and those untreated, *Laroche, Marsan, Bompard and Corcos* (1937) obtained relief of dysuria and polyuria and marked improvement in some cases of incomplete retention; voluntary micturition was re-established in 72 per cent of their patients with chronic complete retention. The results of *Day, Martin, Kutzmann and Kessler* (1938), although not so striking, were distinctly favourable. They concluded that

> "Testosterone is effective in bringing about clinical improvement in a large percentage of patients with benign prostatic hypertrophy, in inhibiting hyperplasia and holding it in check at least temporarily".

Hamilton and Gilbert (1938b), reporting the beneficial results of Perandren therapy in 7 of 11 patients with obstructive symptoms, express the belief that

> "The results obtained with androgenic substance do not seem to be due to changes alone in the prostate; they may possibly be due to increased body vigor and muscular [illegible]
>
> in patients under treatment for long periods of time, and (d) the size of the muscular viscera is increased".

They summarize their findings as follows·

> "Decreased body vigor and muscular tonus are emphasized

as factors in the phenomenon of urinary retention commonly seen in males over 50 years of age. In such patients male hormone substance has been observed to increase body vigor and muscular tonus and to be followed by a decrease in the urological symptoms. It is suggested that some large part of the benefit obtained with male hormone substance is due to effects on parts of the body other than the prostate".

That an effect on the prostate may also be a factor is suggested by a report on the diminution of size which occurred after a massive dose (100 mg. daily for 34 days) of Perandren:

> "The bladder was again opened, and by palpation it was estimated that the prostate had decreased in size. It was judged that the gland was now only a third of its previous bulk". (*Sharpey-Schafer and Shackman*, 1939. See also page 64.)

When Perandren produces amelioration of symptoms in the absence of any noteworthy effect on the prostate itself, the improvement obtained may be due to the increased tonus of the bladder and the detrusor muscles and to the hypertrophy of the urethra which testosterone may cause (*Egger*, 1944).

Summarising, there seems to be some evidence that Perandren produces symptomatic improvement in some cases without necessarily effecting a measurable diminution in the size of the enlarged prostate. It is difficult to assess the divergent results obtained from clinical experiments and no definite conclusion can be reached at present other than that androgenic treatment is harmless, frequently beneficial and therefore worthy of trial. The symptomatic improvement is particularly useful where operation is impossible, and in preparation for surgical treatment. If carcinoma of the prostate is suspected, the use of Perandren is contraindicated.

Dosage: See p. 142.

CARCINOMA OF THE PROSTATE.

It is now well established that œstrogens are of benefit in the treatment of *inoperable carcinoma of the prostate with* metastases, although not a cure. The pioneers of this method of treatment were *Huggins* and his collaborators (1941a, b, c), who found that injections of androgens caused a rise, and

castration or injections of œstrogens a fall, in the serum acid phosphatase. This had previously been shown by *Gutman and Gutman* (1938) to be raised in most patients with metastatic carcinoma of the prostate. As a result of these findings, *Huggins* employed castration or the administration of œstrogen for inoperable prostatic cancer and obtained favourable results. Both castration and œstrogens act mainly by reducing the supply of androgens, but the actual mode of action of œstrogens is uncertain. It is unknown whether they reduce the output of androgen from the testes either directly or indirectly through the anterior pituitary or whether they have a direct antagonistic effect on androgens or an action on the cancer cell itself.

Since the papers of *Huggins* and his collaborators, there have been numerous reports bearing testimony to the beneficial effect of œstrogens. Although it is generally agreed that prostatectomy is the correct procedure in early carcinoma of the prostate, when the disease is confined to the gland, unfortunately this may not always be possible, as symptoms frequently do not arise until metastases have occurred The administration of œstrogens (e.g. Ovocyclin or Eticyclin) to these patients often produces a marked alleviation of symptoms: the local disturbances of micturition improve, pain resulting from metastases is relieved and the metastases may regress considerably. There may or may not be any obvious change in the prostate itself. Patients previously bedridden may gain in weight and subsequently be able to lead fairly active lives. It is important that treatment be continued indefinitely in reduced dosage, but even in spite of continued treatment relapse and subsequent death may occur.

Kearns (1942) and *McCrea* (1946) used ethinyl œstradiol in preference to stilbœstrol in the treatment of prostatic cancer and obtained very favourable results The side-effects of œstrogenic therapy consist of swelling and tenderness of the breasts, pigmentation of the areola, impotence, sterility, loss of libido, irritation of the skin, slight œdema and vertigo (*Fergusson*, 1946). *McCrea* found that the side effects with ethinyl œstradiol were less intense than with stilbœstrol and *Kearns* stated that there is less stimulation of the breast with ethinyl œstradiol and possibly less gastric irritation. Androgens are contraindicated in carcinoma of the prostate as they may accelerate its growth

Dosage: See p. 142.

SEX HORMONES IN THE FEMALE

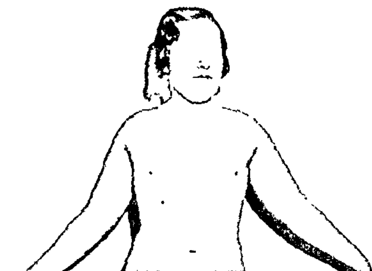
While there are disorders arising in the female in which the use of the female sex hormones, Ovocyclin, Eticyclin, or Lutocyclin, is indicated, there are some which are benefited by the male sex hormone, Perandren. It is therefore considered advisable to point out that its prolonged administration to female patients, [illegible]

changes be observed, the dose should be reduced or the treatment suspended.

AMENORRHŒA
HYPOMENORRHŒA
OLIGOMENORRHŒA.

Amenorrhœa is "usually due to a sub-threshold effect of œstrin on the uterus" (*Bishop*, 1937a). **Primary amenorrhœa** results from failure of development of the ovaries, which may be primary or secondary to deficient secretion of pituitary gonadotrophins, or from an inherent unresponsiveness of the uterus to the action of ovarian hormones. In these cases the uterus is usually small and the endometrium atrophic. In order to build up the uterus to normal size and to bring about proliferation of the endometrium, œstrogens should be given cyclically, either as Eticyclin by mouth in doses of 0·05–0·1 mg. daily for 20 days or as 5 injections of 5 mg. of Ovocyclin at intervals of 3 or 4 days. An œstrogen-withdrawal hæmorrhage may occur about 8 days after the last administration; treatment should be resumed on the day after this has ceased In primary amenorrhœa with a hypoplastic uterus several courses may be necessary before bleeding is produced In the absence of a hæmorrhagic response, an interval of two weeks should elapse before the next course of treatment.

In addition to œstrogens some authorities prefer to give progesterone (Lutocyclin) for a week or ten days during the second half of the cycle. It is started during the latter part of the œstrogen course and is given either as Lutocyclin 'Linguets' in doses of 25–30 mg. daily or as Lutocyclin 10 mg intramuscularly on alternate days.



Patient aged 24, showing failure of development of secondary sexual characteristics. Treatment with gonadotrophic hormones and radiation therapy was unsuccessful



Cyclical therapy with œstrogens and progestogens over a period of two years resulted in cyclical uterine bleeding, breast development and in increase of pubic and axillary hair

Photographs reproduced by courtesy of Rita S. Finkler, M.D., Newark, N.J.

FIG. 11.

If the uterus is infantile, prolonged treatment with œstrogen may be necessary to enable the uterus to attain normal size (*Greene and Robson*, 1948). This may be effected by means of Eticyclin by mouth in doses of 0 05 mg. daily or Ovocyclin P or B in doses of 5 mg. intramuscularly every 5 days. It may be a year before full uterine growth is obtained. Treatment will be unavailing if the uterus is refractory to stimulation.

Kaufmann (1937) stated that the hormonal treatment of primary amenorrhœa does not cause subsequent spontaneous menstruation. This is the experience of most observers (e.g. *Bishop*, 1949) and therefore the treatment of such cases will have to be continued indefinitely. For this reason and because these patients are sterile, some endocrinologists consider treatment unnecessary, but therapy may often be instituted with advantage either for psychological reasons or to improve any symptoms of ovarian deficiency that may exist.

Primary or functional amenorrhœa of puberty *usually* requires no treatment as menstruation often becomes established spontaneously in a year or two, the condition being nothing more than delayed puberty. Treatment, however, should not be delayed too long, as uterine hypoplasia may ensue and be difficult to correct If therefore menstruation fails to occur after a reasonable period, œstrogenic therapy is indicated. Its employment during several cycles may bring about normal menstrual rhythm.

Secondary amenorrhœa may be due to many psychological and general causes. If such a cause is present it should first be dealt with before recourse to endocrine therapy, for its successful [illegible]

(*Greene and Robson*, 1948).

Ethinyl œstradiol (Eticyclin) is as effective as œstradiol benzoate or dipropionate (Ovocyclin B or P) *Birnberg, Livingston, Kurzrok and Sherber* (1947) treated 24 patients with primary or secondary amenorrhœa with 0 05 mg. of ethinyl œstradiol daily for 20 days and in most cases an œstrogen-withdrawal bleeding occurred. They found that larger doses and more prolonged *treatment were usually required in those with primary* amenorrhœa.

Zondek's Rapid Method. A more rapid method of treating amenorrhœa has been devised on the grounds that induction of the initial proliferation of the uterine mucosa by means of œstrogen is unnecessary (*Zondek*, *Rozin* and *Vesell*, 1940). In cases of secondary amenorrhœa of less than two years' standing *Zondek* (1942) obtained satisfactory results by administering in one injection 12·5 mg. of progesterone and 1·25 to 2·5 mg. of œstradiol benzoate on each of two successive days. In cases of more than two years' duration he induced bleeding with a total dose of 50 mg. of progesterone alone distributed over a period of 2 to 5 days. In primary amenorrhœa he found that the 5-day treatment with progesterone failed, but that bleeding occurred if progesterone was combined with œstrogen, 10 mg. of progesterone and 1 mg. of œstradiol benzoate being given daily in one injection for 5 days. In all types bleeding usually occurs 3 to 5 days after the last injection.

Berlind (1943) obtained similar results by this method, although he points out that spontaneous normal menstrual rhythm does not necessarily follow and that in no case of primary amenorrhœa did bleeding take place in subsequent months without therapy. *Finkler* (1944) has also reported success with this method.

Dosage: See p. 143.

ESSENTIAL DYSMENORRHŒA.

There are numerous hypotheses concerning the cause of essential dysmenorrhœa. The view that it is due to increased uterine contractions resulting from an excess of œstrogen or a deficiency of progesterone has been questioned (*Moir*, 1936; *Bishop*, 1947); so also has the hypothesis that it is caused by contractions of an ill-developed uterus (*Bishop*, 1947). *Moir* (1936) has shown that the acme of pain corresponds to the disappearance of pulsation in the uterine artery, suggesting that the pain is due to ischæmia and is analogous to that of angina pectoris and intermittent claudication. The causes of such ischæmia may be numerous, but in some patients it may be brought about by uterine contractions; whether these are due to excess of œstrogen is doubtful. A further view is that it is caused by engorgement of the pelvic vessels leading to compression of the nerve-endings and consequently pain.

Œstrogen Therapy. *Wilson and Kurzrok* (1938) consider that dysmenorrhœa arises only in patients in whom ovulation has occurred and who therefore have a corpus luteum and a secretory endometrium. They advocate the use of œstrogens during the first half of the menstrual cycle and claim satisfactory results in as many as 70 per cent. of their cases. *Sturgis* and *Albright* (1940) support this view and suggest that œstrogen acts by inhibiting the secretion of follicle-stimulating hormone of the anterior pituitary and hence prevents ovulation. *Bishop* (1947), while agreeing that œstrogens relieve some cases of dysmenorrhœa, suggests that they may act by abolishing ischæmia. *Lyon* (1943), however, has followed the basal body temperature (see p. 54) in patients with dysmenorrhœa, ovulation being indicated by a rise of temperature. He found that when ovulation was suppressed by means of œstrogens, dysmenorrhœa did not occur. This effect was achieved by giving 0·05 mg. of ethinyl œstradiol daily by mouth, starting on the 4th or 5th day of the cycle and continuing for 21 to 24 days. Treatment had to be repeated monthly, as relief was not permanent, but in order to avoid producing endometrial hyperplasia, it was omitted for one month in every three.

Progesterone Therapy. Investigators who adhere to the view that excess of œstrogenic hormones causes severe and painful uterine contractions and that the corpus luteum hormone inhibits this effect consider that progesterone is the rational therapy for dysmenorrhœa (*Campbell and Hisaw*, 1936). *Soule* (1941) has stated:

> "There is a general consensus of opinion that this form of therapy (progesterone) gives good results. There is complete relief of dysmenorrhœa in half or more of all patients treated".

Soule treated 28 patients with ethisterone (anhydrohydroxy-progesterone) orally. Twenty of the 28 patients were benefited, an incidence of 71 per cent. He found that the optimum dose was about 60 mg. daily for 5 or 6 days immediately pre-menstrually, but that in no instance was permanent relief obtained.

Greene and Robson (1948) have observed that endometrial biopsies performed on women suffering from dysmenorrhœa point to the conclusion that some of them show no corpus luteum activity and that in many of these the administration

of progesterone is highly effective. They consider that it is more likely to be efficacious in women with feminine physique and a well-developed uterus.

Androgen Therapy. In certain cases of dysmenorrhœa Perandren may be effective. It may act by relieving pelvic congestion. *Salmon, Geist and Walter* (1939) tabulate as follows the results of the treatment of 30 patients complaining of dysmenorrhœa and of ages varying from 15 to 45 years.

(*a*) Results of Treatment of 30 cases.

Satisfactory results	*26 cases*
Complete relief	*22 cases*
Incomplete relief	*4 cases*
Failures	*4 cases*

(*b*) Follow-up of 25 cases.

Symptom-free from 3 to 24 months after cessation of treatment	*14 cases*
Slight recurrence of pain after 2 months ..	*8 cases*

The dosage employed amounted in most cases to 250–300 mg. testosterone propionate given during one cycle, commencing in some cases during the first week and in others on the 15th or 16th day of the cycle. No undesirable effects were produced by this dosage, although the administration of 500 mg. within the same period produced signs of masculinisation. Similar results were reported by *Greenhill and Freed* (1939). *Rubinstein* (1939), discussing the rationale of the use of Perandren in dysmenorrhœa, attributes the good results obtained to the inhibition of follicular maturation and ovulation and a relaxation of the myometrium *Rubinstein and Abarbanel* (1939) summarise the results obtained in the treatment of 26 cases as follows:

> "Testosterone propionate has been found to relieve most cases of essential dysmenorrhœa. It has not been as helpful in organic or anatomically determined dysmenorrhœa."

Of the 26 cases, 16 obtained complete relief, 4 were partially relieved, 4 failed to respond to the treatment and 2 experienced an exacerbation of the symptoms.

Cantor, Vant, Conn and Huston (1942) maintain that "the most effective remedy is found in the androgens". They gave testosterone propionate, 5–10 mg. on alternate days, the first

dose being on the day previous to the usual time of onset and the treatment being continued throughout the period during which symptoms were usually present. *Bishop* (1947) recommends the administration of methyltestosterone throughout the cycle in doses of 10 or 15 mg. daily by mouth, or injections of testosterone propionate 10 mg. on alternate days during the premenstrual and menstrual weeks.

Dosage: See p. 144.

PREMENSTRUAL TENSION.

Premenstrual tension is defined by *Bishop* (1949) as a syndrome of nervous tension, irritability and depression accompanied by a bloated feeling of abdominal distension and sometimes severe headaches and mastalgia. He considers that it is probably due to defective production of progesterone with incomplete inactivation of œstrogen. It has been suggested that progesterone *is essential for the normal metabolism of œstrogen* The symptoms are sometimes relieved by the administration of progesterone or ethisterone or low doses of androgens during the second half of the cycle (*Bishop*, 1949), the rationale of this therapy being that it counteracts the excess of œstrogen.

Dosage: See p. 144.

FUNCTIONAL UTERINE BLEEDING.

Functional uterine bleeding may be defined as uterine bleeding which appears in the absence of gross lesions, at unexpected times and in abnormal amounts (*Richardson et al.*, 1941). All organic causes of irregular uterine hæmorrhage should be excluded before regarding such a case as "functional". The diagnosis of functional uterine bleeding resolves itself into a diagnosis of hormonal disturbance.

Functional uterine bleeding consists of various clinical and [illegible] metrium, [illegible] atrophic [illegible]

(*a*) Hypermenorrhœa, or menorrhagia, which may be defined as prolonged bleeding at the time of menstruation.

(*b*) Polymenorrhœa, i.e. shortening of the menstrual cycles so that bleeding occurs too frequently.

(*c*) Metrorrhagia, or irregular bleedings during an apparently normal cycle.

(*d*) Intermenstrual or mid-cyclical bleeding.

(*e*) Metropathia hæmorrhagica, which is manifested by severe, prolonged and irregular bleeding with long intervals of amenorrhœa.

Functional uterine bleeding may occur at any time between the menarche and the menopause. The ætiological factors are obscure. It may be related to imperfect formation of the corpus luteum, so that the endometrium is subjected to the prolonged action of œstrogen. Bleeding may occur as a result of œstrogen being at the "threshold" or bleeding level; or the œstrogen level may be higher than this, causing a period of amenorrhœa, and bleeding ensues when there is a sudden fall in the level of œstrogen (œstrogen-withdrawal bleeding). The condition may arise in both ovulatory and anovulatory cycles.

Intermenstrual bleeding occurs at about the time of ovulation. There is a disturbance of the hormonal equilibrium between the time of rupture of the Graafian follicle and the formation of the corpus luteum. It is suggested that at this period there is a transient fall in the level of œstrogen and a consequent œstrogen-withdrawal bleeding (*MacGregor*, 1938b).

Metropathia hæmorrhagica is a separate pathological entity. It is associated with failure of ovulation and persistence of the Graafian follicle Characteristic features of the ovaries are absence of active corpora lutea, Graafian follicles in various stages of development and "cystic" degeneration. The endometrium shows hyperproliferation which has not undergone progestational or secretory transformation and the cystic nature of the glands imparts a "Swiss-cheese" pattern to the lesion. Portions of the endometrium become necrotic and are cast off, but in their place renewed growth occurs. It is thought that these changes are brought about by the action of œstrogen which is unopposed through lack of progesterone. There are, therefore, prolonged hæmorrhagic phases for four to eight weeks, followed by periods of amenorrhœa lasting for several weeks.

Functional uterine bleeding may be treated by œstrogens (except in the case of metropathia), progesterone or androgens.

THE EFFECT OF PROGESTERONE ON THE HUMAN ENDOMETRIUM.

Endometrial biopsy from a patient with Anovular Bleeding, showing hyperplastic endometrium before treatment

showing transformation

T N McGregor and the

Œstrogen therapy. "Probably the most dramatic result of the use of sex hormones in gynæcology is the hæmostatic effect produced by œstrogen in cases in which the bleeding has been prolonged and is alarmingly heavy. High doses given every four hours will arrest the hæmorrhage in 24 to 36 hours" (*Bishop*, 1949).

Karnaky (1940), *McGinn* (1942), *Bickers* (1944, 1946) and others have also found that large doses of œstrogens are effective in checking functional bleeding. *Karnaky* has reported that 87 per cent. of his patients, in whom uterine bleeding had been checked with œstrogen, subsequently had normal menstrual periods and *McGinn* made similar observations. Œstrogen acts initially by raising the blood level above that at which bleeding occurs and *McGinn* has suggested that the subsequent normal period is due to the inhibitory effect of œstrogen on the anterior pituitary, so that the ovary is given a period of rest and thereby normal ovarian function and menstruation are restored.

Hamblen, Cuyler, Pattee and Axelson (1941) use œstradiol benzoate or some natural œstrogen to check the bleeding and follow this with cyclical treatment, consisting of the administration of œstrogen during the first half of the cycle and corpus luteum hormone (as progesterone or ethisterone) during the second half. In general this treatment is given until normal cycles are established and is found to be effective in most cases. *McGinn* (1942) has also found a regimen of this type to be most successful.

Bickers (1946) used ethinyl œstradiol in 12 patients with anovulatory metrorrhagia with satisfactory results It was given in doses of 0 3 mg daily for 20 days and bleeding stopped in all patients except one within six days of starting treatment. Progesterone, 5 mg., was injected daily during the last five days of ethinyl œstradiol administration and at the end of this treatment normal menstruation occurred within five days. Subsequently, from the 5th to the 25th day of the cycle the treatment was repeated *Bickers* claims that this treatment over a period of three successive months establishes regular menstruation in about 70 per cent of cases after the treatment is discontinued.

Progesterone Therapy. Progesterone has been successfully used in the treatment of functional uterine bleeding. The rationale of its administration is based on the view that the condition is due to defective secretion of progesterone, so that

(1) the endometrium is subjected to the prolonged action of œstrogen, and (2) complete shedding of the endometrium, which limits menstrual bleeding, does not occur. The complete shedding of the endometrium and consequent curtailment of bleeding as a result of the action of progesterone has been described as a "medical curettage" (*Albright*, 1938). *MacGregor* (1938b) has suggested that progesterone brings about increased elimination of œstrogen by urinary excretion and by conversion into less active forms, so that the blood-level of active œstrogen is reduced. *Smith, Smith and Pincus* (1938) have also postulated that progesterone controls bleeding by inducing normal metabolism of œstrogen.

Greenblatt and Kupperman (1946) have discussed progesterone therapy for the control of menorrhagia They point out that progesterone has been placed in disrepute by a number of clinicians for the treatment of this condition because upon its withdrawal further bleeding ensues; they emphasize that "the progesterone-withdrawal bleeding should not be mistaken for a prolongation or resumption of the menorrhagic syndrome, but should be designated arrest of bleeding according to plan". They write:

> "Arrest of bleeding according to plan may be defined as follows: When progesterone preparations are administered for periods of from three to five successive days, either parenterally in doses of 5 mg. to 10 mg daily, or orally in the form of anhydrohydroxy-progesterone (ethisterone) in doses of from 100 mg. to 150 mg during a period of functional uterine bleeding, hæmorrhage may cease, slow down or continue unabated during therapy. About two or three days after withdrawal of medication the bleeding suddenly may increase, continue for three or four days and then may stop abruptly or taper down and halt slowly In all, uterine bleeding continues for six to ten days after cessation of therapy and closely resembles that of a normal menstrual period. Moreover, this latter phase will be succeeded by the desired period of amenorrhœa. Unless this phenomenon . . . . is appreciated, the clinician may conclude that progesterone therapy increases bleeding and accordingly is contra-indicated".

Progesterone is indicated in the treatment of metropathia hæmorrhagica. *Scowen* (1944) gave 20 mg. of progesterone intramuscularly on alternate days over a period of eight days. He found that bleeding was intensified for four to seven days and then ceased. During each premenstrual week the course was repeated and the dose gradually reduced. Eventually only 5 to 10 mg. were required each month and after six courses menstruation sometimes continued normally without further treatment. He obtained similar results with ethisterone by mouth in a total dosage of 200 mg. during the eight days.

To quote *Bishop* (1949), "Metropathic floodings may be anticipated and prevented by giving progesterone to induce a medical curettage two to three weeks after cessation of the last bleeding episode and therefore before the hæmorrhagic bout is due to begin. Subsequent progesterone-withdrawal bleedings may be induced at any convenient regular interval, such as every 28 days." (Figure 13.)



Prevention of metropathic flooding by rhythmical induction of medical curettage by progesterone

Reproduced by courtesy of Dr P M F Bishop and the Editor of the "British Medical Journal"

FIG. 13.

Androgen Therapy. It has been shown (p 56) that Perandren will arrest the menstrual cycle in monkeys for as long as it is administered, that no harmful effects are demonstrable and that menstruation recurs normally when the treatment is suspended. Testosterone propionate will also inhibit menstruation in the human female (*Papanicolaou, Ripley and Shorr*, 1939); doses of 100–300 mg. per week appear to be necessary to produce this effect (*Spence*, 1939a)

Loeser (1938a) treated 5 cases of menorrhagia, probably due to small intramural fibromata, with testosterone propionate and with doses of 50 mg. on alternate days for two weeks found that the menstrual flow was delayed by 8 to 10 days and was scantier and of shorter duration. With a total dosage of 500 mg. menstrua-

tion was missed altogether and curettage revealed an atrophic endometrium. Five other cases of menorrhagia of unknown ætiology reacted in a similar manner. He concluded that testosterone probably acts by inhibiting the secretion of gonadotrophic hormone by the anterior pituitary, thus preventing ripening of the ovarian follicle.

Foss (1938a) also obtained good results in 16 cases of menorrhagia and metrorrhagia and observed that the treatment brought about inhibition of endometrial proliferation and maintained the endometrium in the resting stage, presumably by inhibiting the production of gonadotrophic hormone. Summarising, he states:

> "Metrorrhagia and menorrhagia can as a rule be controlled by injection of testosterone propionate in adequate doses. The amount required depends on the clinical findings and the pathology of the condition".

Similar results have been obtained by other observers. When given in doses of 25 mg. daily for two or three days, testosterone propionate may control bleeding within 24 hours (*Salmon, Geist, Gaines and Walter*, 1941; *Cantor, Vant, Conn and Huston*, 1942).

Greenblatt and Kupperman (1946) have observed that if hæmorrhage is not satisfactorily controlled with progesterone,

[illegible]

after a progesterone-withdrawal bleeding will occur and will be followed by a normal period of amenorrhœa. The subsequent administration of progesterone before each period will promote normal menstruation

Dosage: See p. 144.

Intermenstrual Bleeding. If the bleeding is slight, treatment may not be necessary. When treatment is indicated progesterone, œstrogens or androgens may be effective. In order to maintain the integrity of the endometrium during the brief period of œstrogen withdrawal, 5 mg. of progesterone may be given daily for 4 days, starting 2 to 3 days before the expected date of bleeding. A similar result may be obtained by compensating for the fall of the œstrogen level by the oral administration of an œstrogen. The third method is to give 10 mg. of methyltestosterone daily for 6 days, starting three

days before the bleeding is due. An argument against the administration of œstrogens and androgens is that they may interfere with the normal course of ovulation. It would appear that progesterone is the more rational form of therapy.

Dosage: See p. 145.

STERILITY.

As in the male, the causes of sterility in the female are numerous and it is beyond the scope of this book to discuss them. A rational method of treating sterility due to failure of ovulation is the administration of gonadotrophic hormones, but their use may be unsuccessful. Small doses of œstrogens sometimes stimulate pituitary activity *Marrian and Butler* (1937) and *Folley and Malpress* (1941), as a result of their work on cattle, are of the opinion that œstrogens undoubtedly cause a reactivation of a quiescent anterior pituitary and in suitable doses stimulate the secretion of gonadotrophins. *Bishop* (1949) has stated that in the treatment of non-ovular infertility œstrogen, followed by œstrogen and progesterone, may stimulate the pituitary to release its gonadotrophins in the correct proportions to induce ovulation. He writes:

> "Three or four courses of low to moderate doses of œstrogen given daily for three weeks, and ethisterone in addition during the third week, with a week's interval between each course, may occasionally be followed by one or two ovular cycles, during which it might be possible for conception to take place".

Œstrogens are indicated if there is reason to believe that sterility is due to under-development or deficient motility of the Fallopian tubes, whereby the ovum fails to enter the uterus.

Defective formation of the corpus luteum leading to progesterone deficiency may result in failure of nidation of the fertilised ovum. Such a condition should be suspected if there is a low urinary output of pregnanediol, the degradation product of progesterone. It is treated by giving Lutocyclin in doses of 10 mg. on alternate days during the second half of the menstrual cycle or 300 mg. of Lutocyclin 'Linguets' throughout the same period.

Brown (1948) is of the opinion that the importance of nidation of the ovum has not been sufficiently stressed; treatment based

tion was missed altogether and curettage revealed an atrophic endometrium. Five other cases of menorrhagia of unknown ætiology reacted in a similar manner. He concluded that testosterone probably acts by inhibiting the secretion of gonadotrophic hormone by the anterior pituitary, thus preventing ripening of the ovarian follicle.

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Greenblatt and Kupperman (1946) have observed that if hæmorrhage is not satisfactorily controlled with progesterone, the combination of 25 mg. of testosterone propionate and 10 mg of progesterone daily for three to five days is often successful. [illegible] be followed by a normal period of amenorrhœa. The subsequent administration of progesterone before each period will promote normal menstruation.

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As in the male, the causes of sterility in the female are numerous and it is beyond the scope of this book to discuss them. A rational method of treating sterility due to failure of ovulation is the administration of gonadotrophic hormones, but their use may be unsuccessful Small doses of œstrogens sometimes stimulate pituitary activity. *Marrian and Butler* (1937) and *Folley and Malpress* (1941), as a result of their work on cattle, are of the opinion that œstrogens undoubtedly cause a reactivation of a quiescent anterior pituitary and in suitable doses stimulate the secretion of gonadotrophins. *Bishop* (1949) has stated that in the treatment of non-ovular infertility œstrogen, followed by œstrogen and progesterone, may stimulate the pituitary to release its gonadotrophins in the correct proportions to induce ovulation. He writes:

> "Three or four courses of low to moderate doses of œstrogen given daily for three weeks, and ethisterone in addition during the third week, with a week's interval between each course, may occasionally be followed by one or two ovular cycles, during which it might be possible for conception to take place".

Œstrogens are indicated if there is reason to believe that sterility is due to under-development or deficient motility of the Fallopian tubes, whereby the ovum fails to enter the uterus.

Defective formation of the corpus luteum leading to progesterone deficiency may result in failure of nidation of the fertilised ovum. Such a condition should be suspected if there is a low urinary output of pregnanediol, the degradation product of progesterone. It is treated by giving Lutocyclin in doses of 10 mg. on alternate days during the second half of the menstrual cycle or 300 mg. of Lutocyclin 'Linguets' throughout the same period.

Brown (1948) is of the opinion that the importance of nidation of the ovum has not been sufficiently stressed; treatment based

upon the assumption that many cases of infertility result from difficulty experienced by the ovum in embedding itself in the endometrium has proved to be successful in an appreciable number of his cases.

Dosage: See p. 146.

THE CLIMACTERIC.

It is perhaps not sufficiently realised that symptoms of the climacteric (change of life) may precede the menopause (cessation of menstruation) by several years and, on the other hand, may occur for the first time some years after a symptomless menopause. In an exhaustive study of the climacteric syndrome in 1,000 patients *Hawkinson* (1938) wrote:

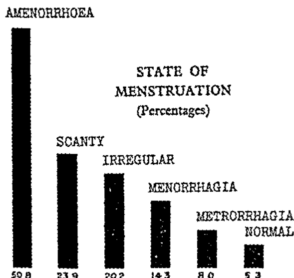
> "The subjective symptoms may appear years before the amenorrhœa and may persist into old age. In 74·3 per cent. of the patients with natural menopause the symptoms appeared months after the amenorrhœa . . . . However, in a small group (5·2 per cent.) the symptoms were delayed from five to twelve years after the cessation of menstruation".

As a result of the observations of numerous investigators it has been established beyond doubt that climacteric symptoms are relieved by the administration of œstrogens (*Bishop*, 1937b; *Hawkinson*, 1938; *Donald*, 1938, *Murless*, 1939). Vasomotor disorders, which are the symptoms most directly referable to œstrogen deficiency, respond most satisfactorily to treatment [illegible] becomes transformed from the menopausal to the œstrous type.

An effective and convenient œstrogen is ethinyl œstradiol (Eticyclin), the most potent of the oral œstrogens. It has the advantage that it is a derivative of the natural œstrogen. *Lyon* (1944) found that the climacteric symptoms—vertigo, hot flushes, sweating, headaches, hypertension, irritability, insomnia, fatigue and leucorrhœa—were controlled with quite small doses of ethinyl œstradiol. Satisfactory relief of symptoms has also been obtained within a few days by other investigators (*Salmon, Geist, Walter and Mintz*, 1941; *Watson*, 1942; *Soule*, 1943; *Harding*, 1944; *Wiesbader and Filler*, 1946).

DATA ON THE MENOPAUSE (Natural) in 841 PATIENTS

AVERAGE AGE at onset of SYMPTOMS .. 40·8 *years*
AVERAGE AGE at onset of AMENORRHŒA .. 44·4 *years*
AVERAGE DURATION of SYMPTOMS .. 37 2 *months*



DATA FROM *Hawkinson* (1938), "The Menopausal Syndrome" *J. Amer. med. Ass.* 111.390.

FIG. 14.

Œstrogen sometimes benefits the arthritic pains which may occur at this time of life. In senile vaginitis œstrogens are specific. *MacGregor* (1938a) reported complete cure in 8 of 15 patients with doses of œstradiol benzoate varying from 10 mg. weekly to 10 mg. daily according to the severity of the condition. The other 7 patients were almost completely relieved of their symptoms. Vaginal suppositories were disappointing, because the atrophic state of the vaginal mucosa did not favour absorption In pruritus vulvæ œstrogens are equally successful. *Hawkinson* (1938) found that 20 of 23 patients obtained complete and lasting relief with this treatment. Ulcerative stomatitis, kraurosis vulvæ and leukoplakia vulvæ are menopausal conditions which, except for leukoplakia, respond well to œstrogen therapy.

Sevringhaus (1944), reviewing endocrine therapy of the climacteric, considers it wise to start with generous doses in order to secure prompt improvement and thereby convince the patient of the value of persisting in the treatment. If relief is not obtained within a week the dose should be increased, otherwise it should be reduced gradually to the minimal effective dose.

Psychic Disturbances: Involutional Melancholia.

The most frequent minor psychic disturbances occurring at the time of the climacteric are excitability, irritability, nervousness, depression and failing memory and power of concentration. Œstrogen treatment may succeed in abolishing these complaints, although mental depression is often refractory. *Harding* (1944) found ethinyl œstradiol to be much more beneficial in the treatment of mental depression at the climacteric than any of the other natural œstrogens he used.

The results obtained in involutional melancholia are at variance, but *Danziger* (1944) considers that there is definitely a group of cases of true hypogonadal deficiency in which specific treatment with œstrogens is capable of giving excellent results. [illegible]

Favourable results in involutional melancholia were previously obtained by *Jones, MacGregor and Tod* (1937), *Hawkinson* (1938) and *Dynes* (1939). The optimal dosage appears to be the equivalent of 5 mg. of Ovocyclin P three times weekly for three

to four weeks, reducing to 5 mg. twice and finally once a week according to the response.

Œstrogen therapy therefore appears to be of no value in anxiety states unconnected with the climacteric, but of considerable value in involutional depressive and anxiety states connected with this time of life. It is not suggested that involutional melancholia is due solely to œstrogen deficit, but that the psycho-somatic disturbance, occasioned by the relatively sudden withdrawal of a hormone having a profound influence on the female economy, may precipitate a psychosis in predisposed cases.

Dosage: See p. 146.

LIBIDO.

Frigidity.

Frigidity may be caused by hormonal or by psychological factors, but does not necessarily arise after castration. Œstrogens are usually ineffective in its treatment, even when they are given in large doses. On the other hand, more consistent results are obtained with androgens. *Salmon* and *Geist* (1943) studied the effect of androgens upon libido in a group of 101 women who were being treated for some endocrine disorder. The androgens were administered as testosterone propionate intramuscularly, as pellets of testosterone implanted subcutaneously or as methyltestosterone orally. All but 13 reported some increase in libido; 20 noted excessive stimulation, which subsided within 2 to 4 weeks after treatment was stopped. The authors conclude that androgens have a threefold action, causing (*a*) an increased susceptibility to psycho-sexual stimulation, (*b*) an increased sensitivity of the external genitalia, particularly of the clitoris and (*c*) a greater intensity of sexual gratification. *Greenblatt* (1943) also observed that the implantation of testosterone propionate in doses varying from 25 to 400 mg restored libido in women in whom it had waned, and concluded that the [illegible]

ointment.

Dosage: See p. 147.

Excessive Libido.

Some women exhibit varying degrees of nymphomania during the premenstrual week and in these endometrial biopsies often reveal an imperfect progestational response of the endometrium. Following the administration of progesterone during the last half of the menstrual cycle there is frequently a decline in sexual urge (*Greenblatt, Mortara and Torpin*, 1942). In a series of 23 women, in whom pellets of progesterone were implanted for various gynæcological disorders, in over one half there was a decided depression of libido, which was particularly marked in several in whom libido had been exaggerated (*Greenblatt*, 1943). It appears that progesterone (and also deoxycortone acetate in larger doses) may suppress sexual desire.

Dosage: See p. 147.

MASTOPATHIA (FIBROADENOSIS) PAINFUL BREASTS.

Desmarest and Capitain (1937a, 1937b) successfully treated chronic mastitis with testosterone acetate and propionate Treatment was initiated 2 days before the anticipated period of pain and was suspended 2 days before the onset of the menstrual flow, recommencing 10 days after its cessation.

They believe that this treatment suppresses the attacks of mammary congestion which precede menstruation; diminishes and arrests chronic mastitis, particularly when of recent origin, causes a diminution or disappearance of adenomatous nodules; reacts favourably on the painful attacks which occur in cystic disease of the breast; is of little use where there are large cysts of long standing; in many cases, particularly in young girls in whom a mutilating operation is to be avoided at all costs, the treatment is of great value.

Turpault (1937) places painful breasts in 3 categories:

(*a*) Pain occurs 8–12 days before onset of menses—due to excess of follicular hormone at the time of ovulation.

(*b*) Pain occurs 3–8 days before the menses—due to a relative excess of progesterone.

(*c*) Pain occurs 1–3 days before the menses—due to relative excess of follicular hormone.

An experience of 53 cases showed that Perandren gave excellent results in groups *a* and *c*, but failed in group *b*.

In groups *a* and *c*, the author suggests, the symptoms were attributable to an excess either of œstrogen or of gonadotrophic hormone. The administration of Perandren successfully counteracted this excess. In group *b*, in which there was a relative lack of œstrogen, small doses of an œstrogenic hormone were given, as Perandren in some cases exaggerated the condition. The usual dose of Perandren employed was 5–10 mg. except in the case of some young girls who were particularly sensitive to the treatment and required only 1–2 mg. daily. Success was often obtained after a period of treatment lasting for one month. Sometimes it was necessary to persist for four months. *Bender* (1937) concurs with *Turpault's* classification of painful breasts He treated 12 cases with testosterone propionate. Apparent cures were obtained in 4, while 6 showed a significant improvement. The 2 failures were in *Turpault's* second category. No harmful effects were observed. *Loeser* (1938a) secured the disappearance of the lumps in 2 cases of chronic mastitis as a result of treatment with testosterone propionate.

A more thorough study of the effect of testosterone propionate in chronic mastitis has been undertaken by *Spence* (1939a, 1939b) The ages of the patients ranged from 19 to 52, the majority being in their fourth decade. In some the pain was continuous, while in others it occurred only in the 7 to 10 days before the period. Half the patients had no palpable abnormality of the breast, while the other half had easily palpable lumps in [illegible]

continuous, but only during the last half of the cycle when the pain occurred only during this phase. The initial dose was 25 mg. twice weekly for a few weeks. This dose was increased if the response was unsatisfactory The total dosage received varied considerably, some patients receiving 100–500 mg, while others received as much as 2,000 mg, or even more. *Spence's* conclusion as to the utility of the treatment is:

"The results with testosterone propionate are promising, in that it brings about dramatic relief of pain and in some instances diminution in the size of the nodules."

He adds that testosterone propionate should be used with caution in women, as signs of masculinisation may appear with high doses. He subsequently found that the inunction of the breast with an ointment of testosterone or testosterone propionate in doses of 3 to 10 mg. of active substance relieved mammary pain in 6 of 8 patients so treated and that because of the small doses required the danger of masculinisation was eliminated. (*Spence*, 1940c)

Dosage: See p. 147.

THREATENED ABORTION, HABITUAL ABORTION.

Progesterone is indicated in the treatment of those cases of threatened and habitual abortion in which there is evidence of a progesterone deficiency, i.e. a diminished urinary excretion of pregnanediol. This may be determined by the Guterman (pregnanediol excretion) test, which is carried out on the early morning specimen of urine and is completed within three hours (*Guterman*, 1944). *Bender* (1948) investigated the value of the test for determining in any given case of threatened abortion whether progesterone should or should not be administered. His findings were as follows:—

(1) Forty-two cases of threatened abortion in which the test was positive, i.e. no evidence of progesterone deficiency; of 11 treated with progesterone, 7 aborted and 4 did not abort; of 31 not treated with progesterone, 6 aborted and 25 did not abort.

(2) Twenty-six cases in which the test was negative, i.e. evidence of progesterone deficiency; of 14 treated with progesterone, 2 aborted and 12 did not abort; of 12 not treated with progesterone, 9 aborted and 3 did not abort.

He quotes *McCormack's* (1946) figures in a series of 30 cases parallel with Group 2, i.e. of 10 treated with progesterone, 2 aborted and 8 did not abort and of 20 not treated with progesterone all aborted.

Bender concludes (1) that there is no indication for treating

with the hormone cases without progesterone deficiency, and (2) that where there is progesterone deficiency the prompt administration of the hormone averts abortion in a large proportion of cases. He writes: "When it does not, it may be that the condition is already irreversible or that there are additional factors present favouring abortion. If, however, progesterone is not given to progesterone-deficient cases, abortion nearly always ensues, although there is a possibility of spontaneous cure".

Bishop (1947) advises injections of 10 mg. of progesterone daily in cases of threatened abortion until the bleeding ceases or until abortion becomes inevitable. Larger doses than this, e.g. 25 mg. daily, may be necessary.

Progesterone has always been shown to be of definite value in the treatment of habitual abortion when this is due to deficiency of progesterone. All observers agree that to be effective it should be started early in pregnancy and continued until about the seventh month. According to *Bishop* (1947, 1949) ethisterone should be given in doses of 30 mg. daily during the second half of each menstrual cycle once pregnancy has been planned and as soon as a period has been missed 200 mg. of progesterone should be implanted as pellets. An alternative method is the intramuscular injection of Lutocyclin in doses of 25 mg. twice a week or ethisterone (Lutocyclin 'Linguets') may be given sublingually.

The combined use of progesterone and œstrogen has been advocated in the treatment of habitual abortion on the grounds that since both hormones are believed to arise from the same sources during gestation, a deficiency of progesterone may be accompanied by a deficiency of œstrogen and that a synergism between the two hormones exists. *Vaux and Rakoff* (1945) employed 10 mg of progesterone and 10,000 rat units (5 mg) of œstradiol benzoate injected together from the one syringe two or three times a week. Treatment was started during the 4th to 10th week of gestation and continued to term. Of 24 patients, who had previously miscarried several times, satisfactory results were obtained in 15.

Dosage: See p. 147.

INDUCTION OF LABOUR, MISSED ABORTION, CARNEOUS MOLE, INTRA-UTERINE FŒTAL DEATH.

In these conditions the administration of 5 mg. of œstradiol benzoate, or the *equivalent dosage of other œstrogens, at four*-hourly intervals increases the sensitivity of the uterus to stimulation by ecbolics or mechanical means. This treatment should be supplemented by the usual methods of induction. In uterine inertia 50 per cent. of all cases appear to derive some benefit (*Jeffcoate*, 1937). This method of accelerating labour has

> "the great advantage of being free from all the dangers that are associated with the administration of other oxytocic substances".

Birnberg, Livingston, Kurzrok and Sherber (1947) used ethinyl œstradiol to influence labour in 49 patients in doses of 0·3 mg. two-hourly up to fifteen doses. Their patients consisted of two groups: (1) those in whom it was desired to induce labour (15 patients), and (2) those who were experiencing a slow non-progressive type of labour (34 patients). In the first group treatment was successful in 10 patients and unsuccessful in 5. In the second group treatment was apparently successful in 30 patients and of no benefit in 4.

After intra-uterine death of the fœtus the level of the blood œstrogen falls. *Jeffcoate* (1940) obtained satisfactory expulsion of the products of conception in 48 of 55 cases after œstrogen administration, which increased the excitability of the uterus.

Dosage: See p. 147.

SUPPRESSION OF LACTATION AND BREAST ENGORGEMENT.

Œstrogen Therapy. *Where conditions exist which render* it desirable to inhibit the secretion of milk or prevent breast engorgement œstrogens may be used with good effect. *Adrian* (1938) found that a single high dose often sufficed to arrest lactation, while in other cases three or four injections were necessary *Foss and Phillips* (1938) used comparatively small doses of œstrone by mouth and found that the results were "consistently satisfactory" in 62 cases; *Barnes* (1942) also obtained good results with small doses of œstrogen. It is, however, the experience of most observers that larger doses are usually

necessary. *Meek and Murby* (1944) found that natural œstrogens by the oral route, in doses of 3·75 mg. every 4 hours for 5 doses, prevented post-partum breast engorgement.

Satisfactory results have been obtained with ethinyl œstradiol orally. *Birnberg, Livingston, Kurzrok and Sherber* (1947) used ethinyl œstradiol in 145 non-nursing post-partum mothers and 26 nursing mothers. They gave 0·1 mg. three times a day for 3 days, then 0·05 mg. three times a day for 3 days and then 0·05 mg. daily for 3 days. In 58 per cent. (85 cases) of the non-nursing mothers breast engorgement was prevented and lactation inhibited for one month following delivery and in 16 per cent. (23 cases) engorgement and leakage were slight. Of the 26 nursing mothers there was partial suppression of lactation in 17 cases and complete suppression in 6 in spite of regular nursing of the infant. *Gershenfeld and Perlmutter* (1948) found that in a series of 501 patients lactation was inhibited or controlled by the use of ethinyl œstradiol more successfully than by any other means. They employed a daily dosage of 1·5 mg. for 6 to 9 days, but later found that equally good results could be obtained with 0·15 mg. daily. *Jeffcoate, Lister, Hargraves and Roberts* (1948) have similarly reported good results in 21 out of 22 cases, using a total dose of 0·75 to 1·3 mg. spread over seven days.

Androgen Therapy. *Kurzrok and O'Connel* (1938) found Perandren remarkably efficacious in the suppression of undesired lactation and the relief of the associated discomfort. Injections of 25 mg. were given twice daily and the symptoms were usually relieved within 24 hours without the employment of any other therapeutic measures.

In a study group of 108 cases, *Beilly and Solomon* (1940) obtained complete inhibition with testosterone propionate in 58 per cent. and incomplete results in 40 per cent. Of the latter, all obtained relief from engorgement and pain in the breasts.

Birnberg, Kurzrok and Klor (1940) in discussing dosage claimed that good results were uniformly obtained when the dose ranged between 125 and 150 mg. testosterone propionate, and that lactation, engorgement and pain did not recur after treatment was stopped. It was considered preferable to divide the total amount into doses of 25 to 50 mg.

These results have been confirmed by other writers, including *Siegler and Silverstein* (1940), who obtained successful cessation of lactation with the alleviation of all symptoms in 47 out of 50 cases. *Kushner* (1942) found the oral form equally effective. He says—

> "Methyl testosterone, orally, can be substituted for testosterone propionate parenterally or percutaneously, for the inhibition of lactation in the post-partum patient".

Dosage: See p. 148.

CARCINOMA OF THE BREAST.

Androgen Therapy. *Loeser* (1938b, 1940) first demonstrated that testosterone propionate may be of benefit in carcinoma of the breast. He described the case of a woman, aged 37, who had a recurrence of carcinoma after removal of the breast. She was treated with injections of testosterone propionate and subsequently with implants of 600 mg. of testosterone propionate at six-monthly intervals. Three-and-a-half years after the inception of treatment she was free from symptoms and signs of cancer. He subsequently reported further cases which were treated with androgens post-operatively and in none was there any evidence of a recurrence five years later (*Loeser*, 1941). Since then numerous observers have confirmed this work. Although testosterone cannot be regarded as a cure of mammary carcinoma, it may in some cases cause temporary regression of the growth, relieve pain and prolong life for months or even years.

Fels (1944) treated 3 patients with 25 mg. of testosterone propionate every other day, giving a total dosage of 750 to 1,550 mg. In 2 with bony metastases there was striking improvement; palpable nodules disappeared and the metastases regressed In the third case the period of observation was too short for a conclusion to be formed *Farrow and Woodard* (1942), however, using smaller doses in 33 patients, obtained equivocal results, although they observed relief of pain in about half of the cases.

Prudente (1945) described the use of testosterone as a postoperative measure to prevent recurrence of mammary cancer. He compared the therapeutic results obtained by treating 65 cases by radical surgery with those obtained by treating 63 cases by radical surgery followed by testosterone propionate. Judged by the survival rate after three, four or five years, there was

almost 100 per cent. improvement in the results for the group treated with testosterone and surgery compared with the group subjected to surgery alone. The author recommends that treatment be continued for five years with gradual reduction of dosage, and concludes that testosterone propionate exercises a protective action against recurrences of surgically treated mammary carcinoma.

Herrmann and Adair (1946) treated 6 cases of carcinoma of the breast with soft tissue metastases. They employed doses of 200 mg. of testosterone propionate injected twice to six times a week, the total dosage ranging from 3,000 to 6,400 mg. The treatment was ineffective except in one patient, who received the largest total dose and in whom there was a striking regression of the lesions.

Boger (1946) has reported a case of a young woman suffering from carcinoma of the breast with extensive metastases in the bones. She was treated by surgical castration and the administration of 1,440 mg. of methyltestosterone by mouth over a period of 8 months. Before treatment she was bedridden; after 2 weeks' treatment she was able to get up and was free from pain. Extensive osteolytic metastases in the spine and pelvis were partially calcified within 6 weeks. The patient died about one year after treatment was begun.

Improvement has also been recorded by *Chase* (1947), [illegible]

to activate their growth, whereas larger doses are beneficial (*Schwander and Marvin*, 1947). One of the patients described by these observers was bedridden on account of severe pain in the leg due to extensive bony metastases. "After the first week of therapy she became ambulatory and several weeks later felt well enough to travel". Ninety days after cessation of treatment calcification of the osteolytic skeletal metastases was demonstrable radiographically. Another "was taking narcotics to relieve pain in her neck and shoulders which was severe enough to confine her to bed. After three weeks of therapy she was able to do without the narcotics and to get out of bed, although she did not become completely ambulatory".

In most patients androgen therapy causes masculinisation, i.e. amenorrhœa, hirsuties and deepening of the voice. These

symptoms disappear gradually on discontinuing treatment. Hypercalcæmia may sometimes be induced by androgens (and also by œstrogens) in patients with osteolytic metastatic mammary cancer and is a serious complication. It causes nausea, vomiting, dehydration and calcinosis of the renal tubules with progressive renal impairment (*Herrmann, Kirsten and Krakauer*, 1949). Patients with bony metastases not infrequently show a hypercalcæmia before sex hormone therapy and in these such treatment is contraindicated. *Adair* (1949) has concluded that in those cases with hypercalcæmia, in which the administration of testosterone makes them very ill, the condition is due to renal damage, the kidneys being unable to eliminate large amounts of calcium. In those receiving sex hormones determinations of the serum calcium and renal function should be made at frequent intervals. The occurrence of listlessness, nausea, vomiting, and increase of the serum calcium or evidence of progressive renal impairment calls for discontinuing sex hormone therapy. The complication is treated by intravenous infusions of 2·5 per cent. sodium citrate solution (*Herrmann, Kirsten and Krakauer*, 1949).

Œstrogen Therapy. As a result of his work on the growth retarding property in certain circumstances of œstrogens and related compounds, *Haddow* and his collaborators investigated the effect of œstrogens on carcinoma of the breast and malignant disease of other organs (*Haddow, Watkinson, Paterson and Koller*, 1944). Of 40 cases of advanced mammary cancer treated with œstrogens, 16 showed temporary retardation, or even partial regression of the growth of the tumour. There was no evidence, however, that the development of metastases was prevented and in spite of the temporary arrest of the disease its ultimate course was unaltered.

That the administration of œstrogens may sometimes produce clinical retrogression of mammary cancer was brought out in a discussion at the Royal Society of Medicine, London (*Discussion* (1944)). The combined results of the ten investigators who spoke are as follows:

Patients aged under 60 years.

No.	*Improved*	*Not Improved*	*Spectacular Improvement*
100	14	86	1

Patients aged 60 and over.

No.	Improved	Not Improved	Spectacular Improvement
68	27	41	5

From this it will be seen that the results are more likely to be favourable in patients over 60.

Herrmann, Adair and Woodard (1947) treated 17 patients suffering from mammary cancer with ethinyl œstradiol and considered that there was a favourable response in 7. It was in women over the age of 60 that improvement was for the most part obtained; in fact, in young women œstrogen therapy appeared to activate growth of the tumour. *Taylor, Slaughter and Preston* (1948), who treated 44 patients with œstrogens and 30 with androgens over a two-year period, also observed that œstrogen therapy produced best results in the older age group and that occasionally it accelerated growth of the tumour. In contrast to androgens, œstrogens caused no regression of bony metastases. *Adair* (1949) has found that œstrogen therapy in many cases requires months before improvement takes place.

There is thus agreement that œstrogens are more effective in older than in younger patients. Their use is also limited on account of the uterine bleeding they may induce and for this reason it is probably advisable to employ them only in patients who have undergone hysterectomy.

Dosage: See p. 148.

GONOCOCCAL VULVO-VAGINITIS IN CHILDREN, LEUCORRHŒA.

The treatment of gonoccal vaginitis with œstrogens may be employed when other methods have failed. The action of œstrogens is (*a*) to promote premature epithelialisation of the vaginal mucosa and (*b*) to acidify the normally neutral or alkaline vaginal secretion. Both these factors are inimical to the continued growth of gonococcus. *Lewis and Adler* (1936) treated 48 cases with suppositories containing 1,000 œstrone units. The suppositories were administered nightly, and the smears became consistently negative in an average of 24·5 days. Fifteen cases recurred, but were cured by resumption of treatment for a further 12 days. All cases developed marked acidity of the vaginal

secretion. No harmful results were seen in any case. The authors reported that "the use of estrin is safe and far more effective than any other treatment that we had tried".

Nabarro and Gordon Signy (1935) obtained good results on daily administration of 1,000–2,000 benzoate units intramuscularly or 4,000 œstrone units orally.

> "The change in the clinical picture is striking—almost dramatic—from the typical thick purulent flux of acute gonorrhœa to a slight, dry, cheesy white discharge. . . . . As a rule the general health of the children was excellent and they put on weight rapidly".

Transitory swelling of the breasts usually occurred during the treatment, but no signs of precocious puberty were observed except in the case of a girl of 10 who developed a slight growth of pubic hair.

Te Linde (1938) found that 16 of 22 children treated by daily œstrogen injections showed characteristic vaginal modifications within an average of 13·5 days and the smears became permanently negative within an average of 17·5 days. The remaining children responded promptly to treatment with œstrogen suppositories.

Berry (1937) investigated the subsequent history of 25 children successfully treated 2 years before by injections of 1,000 œstrone units 3 times a week. Of these, 17 had had no recurrence, 7 recurred within 6 months, and 1 was uninfluenced by the treatment.

Klaften (1937) recommends that leucorrhœa in adults should be treated with œstrogens. This treatment restores the normal adult hydrogen-ion concentration, increases the deposition of glycogen, and encourages the reappearance of the normal vaginal flora.

Dosage: See p. 148.

CONDITIONS COMMON TO BOTH SEXES

PREMATURITY.

The action of testosterone in promoting the anabolism of protein has been referred to on page 70. The resultant effects are increase in growth and muscular hypertrophy. *Shelton, Varden and Mark* (1947) have applied this knowledge to the treatment of premature infants. Seventy-four babies of both

sexes all under 2,000 grams in weight were divided into three groups; one a control, one in which the infants were given 5 mg. of methyltestosterone daily and one in which they received daily intramuscular injections of 4 mg. of testosterone propionate. A distinct shortening in the time required to regain birth weight and in the time required to reach 2,500 grams was observed in both groups receiving testosterone compounds. Four sets of premature twins were included in the study and in every case the infant receiving testosterone gained weight more rapidly than his twin The authors suggest that androgen therapy may be a useful adjunct in the treatment of premature infants needing metabolic stimulation. They found no contraindications to the use of testosterone compounds and no interference with bone growth.

Dosage: See p. 148.

ENURESIS.

Most cases of enuresis appear to be functional in origin and devoid of any disease of the urinary tract or nervous system. A familial tendency, emotional disturbances and improper training may be ætiological factors. There are several favourable reports on the use of androgens in the treatment of the condition. *Ucko* (1946) has suggested that they are effective because they increase the tonus of the bladder, so that the intravesicular pressure at which desire to urinate is experienced is increased, and because they probably augment the tonus of the sphincter muscles.

Zehn (1939) successfully treated 32 women and children suffering from diurnal and nocturnal enuresis with injections of 5 mg. of testosterone propionate daily. *Schultz and Anderson* (1943) reported their results in 50 children aged 3 to 14. One group was given 10 to 25 mg of testosterone propionate intramuscularly daily and the other 10 to 20 mg. of methyltestosterone daily by mouth. They found that 54 per cent. were completely cured, 34 per cent. much improved and the remainder were not benefited.

Kugelmass (1946) treated 75 children of both sexes. They were given 10 to 30 mg. of Perandren 'Linguets' in divided doses daily for one to three months. If sublingual administration produced no significant improvement within two weeks, it was supplemented by a weekly injection of 10 mg. of testosterone

propionate. The fluid intake was restricted. In those that responded nocturnal enuresis diminished in both frequency and urgency in 3 to 10 weeks, but diurnal enuresis was more resistant. As the condition improved testosterone was gradually diminished and the fluid intake slightly increased. Fifty-nine of the children were cured in 3 to 10 weeks, 10 were improved in 15 weeks and 6 were not benefited.

Dosage: See p. 149.

ACNE VULGARIS.

It is well known that androgens are capable of inducing acne in susceptible subjects. On account of this and the frequent occurrence of acne during and just after puberty, it has been postulated that acne is caused by a disturbance of the normal balance between androgens and œstrogens, the androgenic factor predominating (*Lawrence and Werthessen*, 1942). *Hamilton* (1941), however, has concluded that the ability of androgens to produce acne is not proof that they are the sole cause of the condition and considers that other factors and an "innate predisposition to acne" are undoubtedly of great importance.

Lawrence and Werthessen (1942), on the hypothesis that œstrogen would restore the androgen-œstrogen balance to normal, used œstrogens in the treatment of 25 patients (14 females and 11 males) with acne. Fifteen patients (60 per cent.) became entirely free in 2 to 6 months; 2 more, in whom treatment was intermittent, became free in 8 and 9 months and the remaining 8, who were still under treatment all showed improvement. Other observers have not obtained such satisfactory results, while yet others have reported improvement with injections of an inert substance (*Williams and Nomland*, 1937; *Molitch*, 1938).

Dosage: See p. 149.

BUCCAL LEUKOPLAKIA, ULCERATIVE STOMATITIS, SENILE GINGIVITIS.

It has been shown both clinically and experimentally that œstrogens are necessary for the maintenance of a healthy state of the tissues of the mouth (*Ziserman*, 1935; *Ziskin*, 1937). Pre-ulcerative and ulcerative stomatitis may occur in women of any age, but it is commonest in young adults and after the

menopause. Many climacteric patients complain of a dryness or burning sensation in the mouth and this condition may proceed to atrophy of the buccal mucosa and later to hyperkeratosis and leukoplakia (*Richman and Abarbanel*, 1943). Stomatitis may occur in males as well as in females.

There have been several reports of the beneficial effects of œstrogens in these conditions (*Nathanson and Weisberger*, 1939; *Moseley*, 1941; *Richman and Abarbanel*, 1943). *Nathanson and Weisberger* treated 25 women and 13 men with buccal leukoplakia with œstradiol benzoate intramuscularly and œstradiol orally. The majority of the women received 6 injections of 1 mg. of œstradiol benzoate on alternate days and 0·5 mg. of œstradiol daily by mouth. The men, most of whom presented histories of sexual decline, received oral medication only in doses varying from 0·17 to 1·0 mg. of œstradiol daily for 90 to 120 days. The tabulated results were as follows:—

	No.	*Cured*	*Improved*	*Not Improved*
Women ..	25	11	11	3
Men ..	13	5	4	4

Improvement was often apparent about one week after starting treatment by injection and in 4 to 6 weeks when oral therapy alone was employed. The lesions reappeared in 3 to 6 months after therapy was discontinued, but were kept under control with a maintenance dose of 0·17 mg. daily.

Richman and Abarbanel (1943) have reported the effect of œstrogens on atrophy of the buccal mucosa, leukoplakia and gingivitis occurring at the climacteric. They write:

> "The administration of estradiol . . . provides a normal metabolic stimulant to the buccal mucous membrane. The latter develops a normal growth pattern. The prickle cell layer hypertrophies, while the corneal layer becomes keratinized. The leukoplakic areas may tend to shrink. Grossly, the oral mucosa resumes its normal moist bright pink colour
>
> "Clinically, the sensation of burning and dryness disappears, while the gingival bleeding is controlled. These findings have been utilised to good advantage in the management of senile atrophic gingivitis".

Dosage: See p. 149

ATROPHIC RHINITIS.

Mortimer, Wright and Collip (1936) observed reddening and swelling of the mucosa of the middle and inferior turbinate bones of the monkey following the injection of œstrogenic hormone. These changes were produced in males as well as in females and in immature as well as adult animals. As a result of these experiments they treated patients with atrophic rhinitis by the intranasal administration of a solution of œstrogen in oil and obtained clinical improvement (*Mortimer, Wright and Collip*, 1937). These results were confirmed by *Eagle, Baker and Hamblen* (1939) and *Hall and MacLeod* (1942). After preliminary irrigation with physiological saline or a solution of 1:10,000 potassium permanganate, the nose is sprayed twice daily with 0 5 c.cm. of an oily solution containing 1 mg. of œstradiol monobenzoate or dipropionate per c.cm. Although it seems that no changes can be demonstrated microscopically, the unpleasant odour is prevented, the mucous membrane becomes smoother and more hyperæmic and the crusts are diminished or disappear completely.

Dosage: See p. 149.

HYPOPITUITARISM, SIMMONDS'S DISEASE.

The anabolic effects of testosterone have been utilised with success in Simmonds's disease, a condition due to hypopituitarism in which asthenia, easy fatiguability and muscular wasting may be pronounced symptoms. *Werner and West* (1943) reported that·

> "striking subjective, objective and laboratory changes followed the treatment with methyl testosterone of four patients with Simmonds's disease. Clinically, the patients demonstrated renewed vigor, sense of strength and libido and redeveloped secondary sex characteristics".

They demonstrated a persistent gain in weight associated with nitrogen retention *Williams, Whittenberger, Bissell and Weinglass* (1945), who treated 6 patients with Simmonds's disease with deoxycortone acetate, thyroid and testosterone, given orally as methyltestosterone, intramuscularly as the propionate or implanted subcutaneously as pellets, found that in all there was an increase of strength, energy and sense of well-being, the improvement being superior to that obtained with deoxycortone acetate alone.

Simpson (1948), discussing the treatment of Simmonds's disease, writes:

> "In all cases in the present series, testosterone or methyl testosterone caused an increase in appetite, weight, strength, libido and eroticism, and a psychological improvement. It also produced a return of hair in the pubic region, axillæ and eyebrows and a darkening of the hair on the head . . . . A total of 150 mg. of testosterone a week proved to be the optimum dose by injection; or 15 to 30 mg. of methyl testosterone daily by mouth. An implantation of 400 to 600 mg. of testosterone was also effective".

He observed that treatment with œstrogens caused some clinical improvement, but not as great as androgen therapy.

Associated with hypopituitarism and hypogonadism may be an anæmia which does not respond to the usual treatment with iron or liver preparations. *Watkinson, McMenemey and Evans* (1947) have obtained a dramatic improvement in anæmia of this type with liver or iron therapy combined with testosterone propionate, whereas there was no response with iron, liver or thyroid alone. They conclude that testosterone exerts a stimulating effect on the bone marrow and that it is indicated in the anæmia complicating long-standing hypogonadism or

Dosage: See p 149

CUSHING'S SYNDROME.

Many of the disturbances which occur in Cushing's syndrome are probably caused by excessive production by the adrenal cortex of the non-androgenic corticoids, the so-called glycogen corticoids of which corticosterone is an example. *Albright, Parson and Bloomberg* (1941) have suggested that the diabetes of Cushing's syndrome may arise through excessive gluconeogenesis, that is, through the excessive conversion of protein

the osteoporosis and the spontaneous bruising brought about by atrophy of the capillary walls. This hypothesis is supported by the finding of a negative nitrogen balance, indicating that less protein is available for tissue building purposes.

The substance which, par excellence, promotes a positive nitrogen balance and builds up body protein is testosterone. *Albright* and his collaborators have shown that treatment of Cushing's syndrome with testosterone decreases the excretion of nitrogen, phosphorus and calcium and at the same time produces an extraordinary improvement in the clinical picture. The patients gain in weight and strength, the abdomen becomes less prominent, the skin becomes more normal in appearance and the liability to bruising diminishes. It is unfortunate that œstrogen therapy is ineffective, as testosterone will increase any virilism that may be present.

Dosage: See p. 149.

CARDIOVASCULAR DISEASES.

The vasodilator effect of androgens and œstrogens has been mentioned on page 66. It is, however, necessary to bear in mind that no vasodilator can be expected to influence advanced structural changes in blood vessels. This is a factor which explains the divergent results that have been obtained in high blood pressure and other forms of cardiovascular disease.

Œstrogens. *McGrath and Herrmann* (1944) have reported that benefit from œstrogenic therapy in women occurred in 160 out of 163 cases of Raynaud's disease, 29 out of 34 in thrombo-angiitis obliterans, 48 out of 48 of early arteriosclerosis obliterans, 24 out of 26 of acute arterial occlusions and 69 out of 74 of chronic long-standing phlebitis. The response in cases where structural and irreversible disease was predominant over vasospasm was, of course, unsatisfactory. *Walker* (1942) confirmed the beneficial effect of œstrogens in similar cases and observed that the sex hormones appear to be valuable chemotherapeutic substances in essential hypertension, angina pectoris and organic peripheral vascular disease.

On the other hand, *White and Smithwick* (1942) deny that œstrogens will prevent vasospasm in the early stages of Raynaud's disease.

Androgens. *Edwards, Hamilton and Duntley* (1939) observed good results in the treatment with testosterone propionate of an appreciable series of cases of thrombo-angiitis obliterans and arteriosclerosis in men. *Bonnell, Pritchett and Rardin* (1941) obtained significant clinical improvement in 22 out of 23 patients with angina pectoris and coronary artery disease. Good results in 7 out of 9 cases of essential hypertension, angina pectoris and thrombo-angiitis obliterans were reported by *Walker* (1942). In discussing the successful treatment of 7 cases of angina pectoris, *Hamm* (1942) states that testosterone propionate appears to be a valuable therapeutic agent in angina pectoris, the effect of the hormone being mediated through its vasodilator properties.

Lesser (1943) observed a decrease in frequency, severity and duration of attacks in all of 46 cases of angina pectoris, and three years later, analysing his results in 100 cases, he found that 91 per cent. improved for periods ranging from 2 to 34 months. His series consisted of 92 males and 8 females, their ages varying from 34 to 77 years. In the majority 25 mg. of testosterone propionate were injected intramuscularly twice weekly for the first 2 weeks, followed by weekly injections of 25 mg. with an average of 12 injections in the whole series (*Lesser*, 1946).

Waldman (1945) obtained favourable results in 7 of 10 male patients with angina pectoris and concluded that patients with stationary electrocardiograms were more prone to respond to treatment with testosterone propionate than those with evidence of progressively increasing coronary insufficiency.

On the other hand, there have been reports which do not confirm these successes. *Zurrow, Soland, Klein and Goldman* (1942) treated 23 patients suffering from arteriosclerosis obliterans with testosterone propionate in doses of 25 mg. twice a week; 15 patients who did not receive any treatment served as controls. Between the two groups they found no difference in the amplitude of blood vessel pulsation, arterial calcification, rest pain or claudication. *Beaser and Massell* (1942) found only slight improvement in one of 6 men with intermittent claudication receiving testosterone propionate in total dosage of 30 to 225 mg. a week for 6 weeks to 6 months, while *Levine and Sellers* (1946) concluded that testosterone preparations appeared to have no value in the treatment of angina pectoris.

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ADMINISTRATION

However, in a recent resumé of androgenic therapy *Greene* (1949) says, "In the present state of knowledge it can only be said that the treatment is worthy of trial in every peripheral vascular disorder in which spasm plays a part, and that disappointment must be expected occasionally in the most seemingly hopeful cases."

Dosage: See p. 149.

INTRAMUSCULAR INJECTION

It is clear that the ideal in treatment is the reproduction of the regular release of appropriate quantities of hormone, as in the normally functioning gonad. It has been explained in the Biological Section that the absorption and elimination of the "true" male and follicular hormones is too rapid to obtain a maximal response. Esterification, which delays the rate of absorption, is therefore resorted to, with a very great increase in clinical efficiency. It does not alter qualitatively their actions.

Owing to questions of solubility and rate of absorption, oil is the vehicle used in ampoule preparations. If given intramuscularly, injections do not cause pain or irritation, but it is advisable to change the site of injection if repeated administrations are made. As with other oily solutions, the technique of injection is facilitated by the previous warming of the ampoule and syringe.

DEPOT THERAPY

By "depot therapy" is meant the subcutaneous implantation of pellets of steroid hormones (testosterone, œstradiol, progesterone and deoxycortone acetate) or the intramuscular injection of a suspension of crystals of these hormones. The method was introduced by *Deanesly and Parkes* (1937b), who found that not only was a very prolonged action obtained, but also the effectiveness of the hormone per milligramme of substance was much greater than when it was injected in oily solution, due no doubt to its slower absorption. The daily amount of hormone required through the implantation of pellets is about two-thirds of the amount necessary when supplied by daily injections of the oily solution.

Bishop (1938) was the first to describe the use of the technique for clinical purposes and subsequently many investigators have confirmed its value. The method provides a slow and continuous supply of the hormone over a prolonged period and therefore is of value in those conditions in which cyclical therapy is not required and in which treatment has to be maintained for many months or for an indefinite length of time. It has the advantage of being economical and of obviating the necessity

on by the Incisional Method.

ision is made in the skin 1 to 1½ inches in length and dissection small pockets about an inch deep are made ıbcutaneous tissue. Each pocket is for the reception llet, so that the implants are separated from each other. uld be taken that there are no bleeding points. Into :et a pellet is dropped from the glass tube and is gently) the bottom with a pair of blunt dissecting forceps. ıd is then closed with two or three sutures and covered 'essing by means of strapping.

Involved in the Rate of Absorption of Implants.

ation concerning the rate of absorption of implants obtained experimentally only from pellets inserted lly, since it is only these which can be conveniently from time to time to be examined, cleaned and weighed. of absorption depends on several factors—the species ipient, the site of implantation and the chemical nature cal characteristics of the pellet. All other factors being , the rate of absorption depends on the surface area o the action of the tissue fluids (*Deanesly and Parkes*, *ımens*, 1941; *Greenblatt and Hair*, 1942; *Bishop and* 44; *Shimkin, Lorenz, Wyman and Norton*, 1944). As ı proceeds and the surface area is reduced, the rate of ı diminishes. The surface area depends on the volume of the pellet. Although the rate of absorption is greater ge pellet than from a small one, proportionately it is ce, a higher level of dosage is obtained from two 'n from one pellet equal in weight to the two.

riments with œstradiol, progesterone, testosterone and

of frequently taking tablets or of receiving injections which are time-consuming and often an inconvenience.

Technique of Implantation.

Implants of the steroid hormones are supplied in small cylindrical blocks of 5 mm. diameter. They are suitable for both methods of implantation in common use to-day: either with Dusseau's "injector" or by insertion using forceps. The "injector" method is to be preferred, since it produces the minimum of trauma and scarring.

The pellets are implanted in the subcutaneous tissue of the anterior abdominal wall, usually above the pubes. Strict asepsis is necessary, otherwise the pellets may subsequently be extruded, sometimes they are extruded even in the absence of sepsis, some hormones, being rather more prone to this than others. The skin is cleaned with a suitable antiseptic solution and the site of operation infiltrated with a local anæsthetic, e.g. Nupercaine-Adrenalin solution.

The pellets are already sterilised and each is contained in a sterile-sealed glass tube between plugs of cotton-wool to prevent it from being shaken and damaged. With the aid of a file the tube is snapped across one of the plugs, which is removed, thereby withdrawing with it any minute particles of glass that may be present. The pellet should not be removed at this stage.

Insertion by the Injector.

The injector consists of a blunt-ended trocar and a cannula of a bore just sufficiently wide to take a cylindrical pellet (diameter 5 mm); the upper end of the cannula widens into a cup to receive the pellet. A small incision slightly longer than the diameter of the cannula is made in the skin with a tenotomy knife and the trocar and cannula are pushed through the incision at an angle of about 45 degrees into the subcutaneous tissue. The trocar is withdrawn, the pellet is dropped into the cup of the cannula by inverting the glass tube containing it and is pushed into the subcutaneous tissue by means of the trocar. The position of the cannula is changed and a second pellet inserted. In this manner several pellets may be implanted in different positions. The instrument is then removed, the edges of the incision are approximated with a hair suture and the wound is covered with a small dressing.

Insertion by the Incisional Method.

An incision is made in the skin 1 to 1½ inches in length and by blunt dissection small pockets about an inch deep are made in the subcutaneous tissue. Each pocket is for the reception of one pellet, so that the implants are separated from each other. Care should be taken that there are no bleeding points. Into each pocket a pellet is dropped from the glass tube and is gently pushed to the bottom with a pair of blunt dissecting forceps. The wound is then closed with two or three sutures and covered with a dressing by means of strapping.

Factors Involved in the Rate of Absorption of Implants.

Information concerning the rate of absorption of implants can be obtained experimentally only from pellets inserted superficially, since it is only these which can be conveniently removed from time to time to be examined, cleaned and weighed. The rate of absorption depends on several factors—the species of the recipient, the site of implantation and the chemical nature and physical characteristics of the pellet. All other factors being constant, the rate of absorption depends on the surface area exposed to the action of the tissue fluids (*Deanesly and Parkes*, 1938; *Emmens*, 1941; *Greenblatt and Hair*, 1942; *Bishop and Folley*, 1944; *Shimkin, Lorenz, Wyman and Norton*, 1944). As absorption proceeds and the surface area is reduced, the rate of absorption diminishes. The surface area depends on the volume and shape of the pellet. Although the rate of absorption is greater from a large pellet than from a small one, proportionately it is less. Hence, a higher level of dosage is obtained from two pellets than from one pellet equal in weight to the two.

In experiments with œstradiol, progesterone, testosterone and deoxycortone acetate *Deanesly and Parkes* (1943) have found that pellets made by compression are absorbed at about the same rate as those made by fusion.

As a result of the implantation, a connective tissue capsule forms in time around the pellet, but how much this capsule interferes with absorption is doubtful. *Geist, Walter and Salmon* (1940) concluded that the capsule prevents absorption, but this contention is not supported by *Emmens* (1941) or by *Bishop and Folley* (1944), who have shown that the slowing up of absorption can be completely accounted for by the reduction in surface area as absorption proceeds. Another change which occurs is

of frequently taking tablets or of receiving injections which are time-consuming and often an inconvenience.

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be expelled in the usual manner. The syringe is then gently agitated with the needle pointing vertically downwards and the injection is made immediately into the gluteal region with the patient recumbent About 1·8 c.cm. of the suspension are injected at first and then, in order to avoid as far as possible any crystals remaining in the syringe, the piston is slightly withdrawn and pushed forward immediately to complete the injection.

In spite of these procedures some crystals may remain in the ampoule and syringe, but this is of no importance since the ampoules contain a corresponding excess of hormone to make up for the loss.

Clinical Applications of Depot Therapy.

PERANDREN.

Depot therapy with Perandren is indicated in eunuchism, eunuchoidism, impotence and Simmonds's disease.

It is advisable to start treatment with intramuscular injections of Perandren and to institute depot therapy after the maintenance dose has been established. From one pellet of 100 mg. the average daily absorption is at first about 1 mg. a day, falling to about 0·5 mg by the 100th day. Patients with complete androgenic failure require the implantation of amounts of Perandren varying from 400 to 800 mg. This produces symptomatic relief for 4 to 6 months.

Perandren 'Crystules' may be employed instead of pellets, injections being necessary every few weeks. In hypogonadism the waning of potency may be taken as an indication for a further implantation or injection.

LUTOCYCLIN.

Depot therapy with Lutocyclin is indicated in habitual and threatened abortion.

In cases of threatened abortion it is recommended that depot therapy be employed only after the hæmorrhage has been arrested by daily intramuscular injection of 10 mg of Lutocyclin in oily solution Since pellets of progesterone are liable to be extruded, they should be implanted as deeply as possible Progesterone is absorbed at an average rate of about 20 per cent. per month (*Warwick and Parkes*, 1940), so that a pellet will

the formation of a protein deposit within the interstices of the pellet (*Folley*, 1942), but *Deanesly and Parkes* (1943) obtained no evidence that this slowed up absorption.

With the diminishing surface area and consequent diminishing rate of absorption the daily amount of hormone which the patient receives is less during the second half of the life of the pellet than during the first. In practice this appears on the whole to be immaterial, for measures should be taken for a further implantation when the effect of the initial implantation is seen to be declining. *Shimkin, Lorenz, Wyman and Norton* (1944) have demonstrated the difficulty in achieving a constant absorption rate from a single implantation and have shown that this can be approached by the periodic re-implantation of additional pellets.

Treatment with 'Crystules'.

A 'Crystule' is an ampoule containing the crystalline hormone in buffered isotonic, aqueous suspension and is employed for intramuscular injections. The crystals form a depot from which the active substance is gradually absorbed and are used in those conditions in which a fairly prolonged therapeutic action is desired. The effect of the injection of crystals lasts for several weeks, in contrast to pellets which exert their action for several months.

After the crystals have been prepared, they are sieved through a mesh of 0·1 to 0·3 mm. Since it is possible for an individual crystal exceeding these dimensions to pass through this mesh, the absolute minimal diameter of the needle used for their injection should be 0·5 mm., but one of 1 mm. in diameter is more satisfactory. A No. 17 S.W.G. serum needle will be found to be suitable.

It will be observed that the crystals sink rapidly to the bottom of the ampoule Before use the ampoule should be thoroughly shaken to displace any crystals which may be present in the neck. After the ampoule is opened, it is gently shaken in order to maintain the crystals in suspension and the contents are quickly withdrawn into the syringe. Any crystals that adhere to the sides of the ampoule should be dislodged by returning some of the liquid into the ampoule and immediately withdrawing it into the syringe. Any air aspirated into the syringe should

be expelled in the usual manner. The syringe is then gently agitated with the needle pointing vertically downwards and the injection is made immediately into the gluteal region with the patient recumbent. About 1·8 c cm. of the suspension are injected at first and then, in order to avoid as far as possible any crystals remaining in the syringe, the piston is slightly withdrawn and pushed forward immediately to complete the injection.

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Progesterone is absorbed at an average rate of about 20 *per cent.* per month (*Warwick and Parkes*, 1940), so that a pellet will

last for several months. Since there is no clinical method of determining when absorption is coming to an end, other than by the estimation of the urinary pregnanediol, which is not entirely reliable, it is advisable to implant one pellet at intervals of two months. By this means the amount of hormone absorbed is kept at a high level.

When treatment with 'Crystules' is employed, the contents of one ampoule should be injected at intervals of two or three weeks.

The results of treatment of threatened and habitual abortion with progesterone alone are conflicting. It is believed that œstrogen as well as progesterone is necessary to prevent abortion (*Vaux and Rakoff*, 1945). It is probable, therefore, that more satisfactory results will be obtained by the additional implantation of one pellet of Ovocyclin at the beginning of treatment.

OVOCYCLIN.

Depot therapy with Ovocyclin is indicated for deficiency symptoms at the climacteric or after castration and for any other conditions in which a prolonged action is desired.

The implantation of a single pellet is usually sufficient to bring about relief of symptoms for 6 to 9 months or more, the rate of absorption being slow. In the presence of an intact uterus greater amounts than this are contraindicated, since excessive hyperplasia of the endometrium and uterine hæmorrhage may be produced. For the same reason, when treatment with 'Crystules' is employed, injections should not be given at more frequent intervals than three or four weeks and no more than one 'Crystule' should be used at a time.

There are no data on depot therapy in carcinoma of the prostate, but the method may prove to be convenient and effective. Since the dosage of œstrogens in this condition should be high, four or five pellets (a total of 80–100 mg.) should be implanted and in some cases an even greater amount than this may prove to be necessary.

SUBLINGUAL ADMINISTRATION

The advantages of oral administration are sufficiently obvious not to require recapitulation. The activity of most of the natural hormones of the steroid group when swallowed is negligible because they are metabolised by the liver or destroyed by the intestinal enzymes. Chemical modifications such as methyltestosterone, ethisterone and ethinyl œstradiol are more resistant to these influences and the degree of inactivation is much less.

When, however, these substances are absorbed from the buccal mucosa, they pass directly into the systemic circulation and thus reach the target organs with comparatively little impairment of their activity. The ability of the liver to inactivate, for example, testosterone, methyltestosterone or ethinyl œstradiol, has been demonstrated by the experiments of *Biskind* (1940), *Burrill and Greene* (1946) and *Segaloff* (1944). *Walton* (1944), who carried out tests on many drugs to demonstrate their effectiveness by sublingual absorption, found that their penetration through the buccal mucosa was a selective process determined by the fat/water distribution coefficient of the particular drug. The steroid hormones, being fat soluble, can penetrate readily, hence their sublingual effectiveness

Patients should be instructed to place the 'Linguet' either beneath the tongue or between the cheek and the gum, and to allow it to dissolve in position, swallowing as little saliva as possible. Absorption from beneath the tongue may be more rapid than from the cheek position, but the latter is found by many patients to be more convenient and comfortable. The time taken for complete absorption depends to quite a large extent upon such factors as the amount of movement inside the mouth, and it varies between 15–60 minutes 'Linguets' are pleasant in taste.

Many workers have published reports confirming the effectiveness of sublingual administration of the sex hormones, for example, *Dunn* (1946) summarising the advantages of Perandren 'Linguets', said:

> "The Linguet form of administration permits a gradual and efficient method of absorption of methyl-testosterone. It is a pleasant, convenient and generally applicable form of testosterone treatment, irrespective of the age of the

> patient . . . . By spreading the dosage throughout the day, one can better maintain a plan of therapy which attempts to approach the normal secretion output of the testes."

The following table of the results achieved by *Lisser and Curtis* (1943) with Perandren "Linguets" in male hypogonadism demonstrates clearly the advantage over the oral administration of methyltestosterone.

CASE NO.	DAILY SUBLINGUAL MAINTENANCE DOSE	DAILY ORAL MAINTENANCE DOSE.
1	20 mg.	30 mg.
2	10 mg.	30 mg.
3	5 mg.	30 mg.
4	5 mg.	30 mg.
6	5 mg.	10 mg.
10	5 mg.	100 mg.

It is interesting to note that in the majority of these cases, as low a dosage as 5 mg. daily was adequate for maintenance therapy. In the six other cases of the same series, no direct comparison was available, but 5–15 mg. sublingually was an adequate daily dose.

Similar results have been reported by other investigators. For example, *Spence* (1942) found Perandren 'Linguets' 10 mg. daily to be sufficient to maintain potency in a eunuch. *Finkler* (1947) in describing the successful treatment of 12 cases of hypogonadism, reported the daily sublingual dose as varying from 10 mg. to 30 mg. *Harding* (1948) used Perandren 'Linguets' in a group of 58 boys aged 7–15 years and obtained extremely good results with *1·25 mg. to 10 mg. daily.* This series included four cases of cryptorchidism and two of enuresis. *Dunn* (1946) comments particularly on the fact that young patients can be instructed to use 'Linguets' correctly

[illegible]

confirming the earlier work of *Joel* (1942), who arrived at a similar ratio of activity by comparing both methods with the intramuscular injection of progesterone. Œstradiol sublingually

has similarly been assessed against its esters used intramuscularly and the ratio has been found to vary between 1:1 (*Hall*, 1949) and 1:2–3 (*Joel*, 1942). Comparative details on ethinyl œstradiol, which is rapidly becoming the most widely used œstrogen in clinical practice, have only recently become available. *Segaloff* (1949) used *Allen's* (1944) method of evaluating the potency of œstrogens, which consists of determining their ability to produce withdrawal-bleeding when they are given to ovariectomised women. He observed that ethinyl œstradiol when injected intramuscularly was five times more potent than when given by mouth. This indicates a substantial degree of inactivation when the latter method of administration is employed and, as stated earlier, the use of 'Linguets' will avoid this partial destruction of the hormone.

PERCUTANEOUS INUNCTION

It had been known for some time that the pure male hormones were highly active if applied locally to the capon's comb, when *Moore, Lamar and Beck* in 1938 made a detailed study of the effects of testosterone, testosterone propionate and œstradiol ointments. It was demonstrated that daily applications provided a complete substitute in experimental animals for the natural secretion of the surgically removed gonads. *Loeser* (1937), *Salmon* (1938a) and *Foss* (1938b) showed that similar effects were obtained in clinical medicine and confirmed that a systemic effect is readily obtainable.

The use of ointments to obtain a general effect is rather laborious, particularly as effective oral forms are available as 'Linguets.' It is therefore suggested that their main use should be where a local effect is desired, e.g Perandren Ointment in chronic mastitis. *MacBryde* (1939) says—

> "ointments (œstrogenic), unit for unit, were more effective in producing breast growth than injections."

Similarly, the local application of an ointment of testosterone to the penis of rats was found by *Greene and Wigodsky* (1938) to cause the same growth of the organs as was caused by similar quantities by subcutaneous injection.

The best results will probably be obtained from the frequent inunction of small quantities, rather than from the infrequent

inunction of larger quantities, even though the total dosage employed be the same in each case. It is advisable to wash the parts used for inunction with soap and warm water to remove superfluous grease and dirt and to rinse well with clean warm water. Gentle scrubbing with a soft nailbrush probably facilitates absorption by the removal of dead epidermal tissue and the induction of a slightly increased vascularity. The skin should be dried and the ointment rubbed in very thoroughly until there is no longer a greasy appearance. If used for a general effect, the abdomen and the thighs are the best sites for application. If the ointments are applied to the patient by another person, the possibility of absorption of the hormone by the skin of the operator's fingers should not be ignored. The use of rubber gloves avoids this possibility.

AVAILABLE FORMS

ANDROGENIC.

Testosterone and its derivatives are available in the following forms:—

(*a*) **Perandren Ampoules** contain testosterone propionate B.P. in concentrations of 5 mg., 10 mg., 25 mg. and 50 mg. in 1 c.cm and 100 mg. in 2 c.cm. ampoules. Rubber-capped vials of 10 c.cm. are also available containing 50 mg./c.cm. A long experience has confirmed the earlier experimental work, which demonstrated that the administration of the propionic acid ester of testosterone gave results far superior to those obtained with the free hormone.

(*b*) **Perandren 'Crystules'** contain 50 mg. crystalline testosterone propionate B P. in 2 c.cm. aqueous suspension with 2 mg. Nupercaine for local anæsthesia. A single intramuscular injection produces effects lasting several weeks. Where prolonged administration is required, 'Crystules' provide a convenient form of depot therapy. The technique of administration is simpler than implantation, but the duration of effect is less prolonged. Their use and indications have been described in the section on Depot Therapy (p.125).

(c) **Perandren Implants** contain 100 mg testosterone B.P.C. in compressed cylindrical blocks of 5 mm. diameter. Subcutaneous implantation produces effects lasting several months. This method of administration is to be preferred for patients who require prolonged treatment, as it is more economical and avoids frequent injections of oily solution. Their use and indications have been described in the section on Depot Therapy (p. 125).

(*d*) **Perandren 'Linguets'** each contain methyltestosterone B.P. in strengths of 5 mg., 10 mg, 25 mg. and 50 mg. Administered sublingually the effectiveness of methyltestosterone is at least double as compared with the oral route In clinical practice it has been found that the dosage of methyltestosterone required by sublingual administration is approximately four times that of testosterone propionate by intramuscular injection. With the strengths now available it is possible to treat many conditions by sublingual therapy alone, but it is often desirable to initiate treatment by injecting the oily solution which produces a more intense effect. The 10 mg. Perandren 'Linguets' are suitable for maintenance therapy in eunuchism and eunuchoidism, while the 25 mg. and 50 mg. concentrations may be used in patients with carcinoma of the breast, for whom frequent injections may be undesirable. For maintenance purposes in the latter cases, a suitable dose is four 50 mg. 'Linguets' daily (equivalent to a daily injection of 50 mg.).

In menorrhagia which does not respond to Lutocyclin treatment, Perandren 'Linguets' in doses of 100 mg. daily for three days often prove effective.

(*e*) **Perandren Ointment** contains 2 mg. testosterone B.P.C. per g. The free hormone and not an ester is used because absorption through the skin is already sufficiently slow and the only object in esterification is to reduce the rate of absorption. The dosage expressed as mg. of testosterone is the same as, or slightly greater than, that of Perandren Ampoules in mg. of testosterone propionate. A 2-inch (5 cm.) strip of ointment contains approximately 1 g. (2 mg testosterone).

ŒSTROGENIC.

Œstradiol and its derivatives are available in the following forms:—

(*a*) **Eticyclin 'Linguets'** contain ethinyl œstradiol 0·01 mg. and 0·05 mg. This is the most potent oral œstrogen in its most economical form. It is of particular value in the treatment of menopausal disturbances in which doses as low as 0·01 mg. daily are often adequate.

Eticyclin scored tablets of 1 mg. are available for conditions which may require high dosage, for example, prostatic carcinoma, mammary carcinoma and induction of labour.

(*b*) **Ovocyclin P Ampoules** contain œstradiol dipropionate B.P. in concentrations of 1 mg. and 5 mg. per c.cm. The dipropionate was found to be the most efficient ester of œstradiol.

(*c*) **Ovocyclin B Ampoules** contain œstradiol monobenzoate B.P. in concentrations of 1 mg. and 5 mg. per c.cm.

(*d*) **Ovocyclin 'Crystules'** contain 10 mg. crystalline œstradiol monobenzoate B.P. in 2 c.cm. aqueous suspension with 2 mg. Nupercaine for local anæsthesia. A single intramuscular injection produces effects lasting several weeks. Where prolonged administration is required, particularly in menopausal cases, 'Crystules' provide a convenient form of depot therapy. The technique of administration is simpler than implantation, but the duration of effect is less prolonged. (See Depot Therapy section, p. 125.)

(*e*) **Ovocyclin Implants** contain 20 mg. of œstradiol B.P.C. in compressed cylindrical blocks of 5 mm. diameter. Subcutaneous implantation produces effects lasting several months This method of administration is to be preferred for patients who require prolonged treatment as it is more economical and avoids frequent injection of oily solution. (See Depot Therapy section, p. 125.)

(*f*) **Ovocyclin 'Linguets'** contain œstradiol B.P.C in concentrations of 0·04 mg., 0·1 mg. and 1 mg. When employed alone, the dosage in mg. should be five times as great as that of Ovocyclin P or Ovocyclin B.

(g) **Ovocyclin Ointment** contains 0·1 mg. (1,000 units) œstradiol B.P.C. per g. in a suitable ointment base. The dosage expressed as mg. of œstradiol is approximately the same as that of Ovocyclin P or Ovocyclin B Ampoules expressed as mg. œstradiol dipropionate or monobenzoate. A strip of 2 inches (5 cm.) of the ointment contains approximately 1 g. (0·1 mg. œstradiol).

PROGESTOGENIC.

(a) **Lutocyclin Ampoules** contain progesterone B P. in concentrations of 2 mg., 5 mg., 10 mg. and 25 mg. per c.cm. Rubber-capped vials of 10 c cm are also available containing 25 mg./c cm. The free hormone and not an ester is used.

(b) **Lutocyclin 'Crystules'** contain 50 mg. crystalline progesterone B.P. in 2 c cm. aqueous suspension with 2 mg. Nupercaine for local anæsthesia. A single intramuscular injection produces effects lasting several weeks. (See Depot Therapy section, p. 125.)

(c) **Lutocyclin Implants** contain 100 mg. progesterone B.P. in compressed cylindrical blocks of 5 mm. diameter. Subcutaneous implantation produces effects lasting several months. This method of administration is to be preferred for patients who require prolonged treatment as it is more economical and avoids frequent injections of oily solution. (See Depot Therapy section, p. 125.)

(d) **Lutocyclin 'Linguets'** each contain ethisterone B P (anhydrohydroxy-progesterone) in strengths of 5 mg., 10 mg. and 25 mg. Administered sublingually the effectiveness of ethisterone is at least doubled as compared with the oral route The ratio of activity to parenteral progesterone is 1:4–6, so that the dosage in 'Linguets' in mg of ethisterone should be 4 to 6 times greater than that of Lutocyclin ampoules in mgs of progesterone. The 'Linguets' may in many cases entirely replace the ampoules, and in others will be found to be convenient for maintenance and supplementary treatment. It is advisable to spread the daily dose of 'Linguets' as evenly as practicable over 24 hours.

DOSAGE

IN THE MALE

GROUP.	TREATMENT.	PRINCIPLE.
Hypogonadism, Eunuchism. (See p. 76.)	**Perandren Ampoules** 25—50 mg. two or three times a week for some months to restore or develop secondary sexual characteristics. For maintenance: **Perandren 'Linguets'** 10–25 mg. daily. (See Depot Therapy Section.)	Promotion of the development of the genitalia and the secondary sexual characteristics by replacement of the deficient or absent internal secretion of the testes.
Cryptorchidism. (See p. 78.)	**Perandren Ampoules** 10–25 mg. twice a week or **Perandren 'Linguets'** 10–25 mg daily.	Promotion of the growth of the structures of the cord and the production of a larger and more pendulous scrotum which is adequate to retain the testes.
Where operation is necessary.	**Perandren Ampoules** 10–25 mg. weekly for a few weeks before operation.	Promotion of the growth of cord structures and scrotum in order to provide a more favourable terrain for surgical treatment
Post-operatively.	**Perandren Ampoules** 10–25 mg weekly for a few weeks after operation or **Perandren 'Linguets'** 10–25 mg. daily.	To discourage post-operative tension and retraction.
Impotence where there is an underlying endocrine defect. (See p. 79.)	**Perandren Ampoules** 25–50 mg two or three times a week For maintenance **Perandren 'Linguets'** 10–25 mg. daily. (See Depot Therapy section.)	Replacement of a defective internal secretion of the testes.

GROUP.	TREATMENT.	PRINCIPLE.
Impotence of purely psychic origin. (See p. 80.)	**Perandren Ampoules** 10 mg. three times a week or **Perandren 'Linguets'** 10–20 mg. daily.	The re-inforcement of libido and the production of erection with the object of restoring the patient's confidence in his own capacities. (N.B.—Higher doses may depress spermatogenesis)
Premature *Ejaculation.* (See p. 80.)	**Eticyclin 'Linguets'** *0 01 mg.* once or twice daily.	See p. 80.
Sterility due to impaired spermatogenesis. (See p. 81.)	**Perandren 'Linguets'** 5–10 mg daily or **Perandren Ampoules** 5 mg. three times a week.	In these dosages the male hormone stimulates spermatogenesis.
Chronic Hæmospermia. (See p. 83.)	**Eticyclin 'Linguets'** 0 05 mg. three times weekly to twice daily.	Depression of the secretions of the seminal vesicles.
Male Climacteric. Premature Senility. *(See p. 83.)*	***Perandren 'Linguets'*** 10–50 mg. daily or ***Perandren Ampoules*** *10–25 mg.* once to three times weekly.	*Restoration of endocrine equilibrium by replacement of testicular hormone.*
Prostatic Hypertrophy, Cases of mild and moderate degree, Inoperable cases. (*See p. 85*)	**Perandren Ampoules** 10–25 mg. twice to three times weekly. For maintenance· **Perandren 'Linguets'** 10–50 mg. daily	Promotion of increased tonus of the bladder and detrusor muscles and enlargement of the urethra, *together with improvement in the general condition.*
Where *operation* is necessary.	**Perandren Ampoules** 10–25 mg twice to three times weekly or **Perandren 'Linguets'** 10–50 mg. daily, starting several weeks before operation	The production of temporary improvement in the local and general condition as a preparation for surgical treatment.
Carcinoma of the Prostate. (*See p. 86.*)	**Eticyclin 'Linguets'** 0 1 mg.–1 mg. three times *daily; after full response* reduce to 0 05 mg two to four times daily.	*Suppression of androgenic effect.*

IN THE FEMALE

GROUP.	TREATMENT.	PRINCIPLE.
Primary Amenorrhœa. (See p. 88.)	**Eticyclin 'Linguets'** 0·05 mg. once or twice daily for 17 days, with intervals of 10 days or **Ovocyclin P Ampoules** 5 mg twice weekly for five injections, followed by an interval of two weeks. The courses to be given over a number of cycles.	An intensive stimulus to the development of the uterus, vagina and secondary sexual characteristics. *Intervals* between courses allow for the occurrence of withdrawal bleeding.
Primary Amenorrhœa associated with infantilism. (See p. 88.)	[illegible] ment with **Eticyclin 'Linguets' or Ovocyclin P Ampoules** as above.	To promote develop- [illegible] erus, [illegible] dary [illegible] stics. [illegible] scer- [illegible] d [illegible] h the [illegible]
Secondary Amenorrhœa, Oligomenorrhœa, Hypomenorrhœa. (See p. 88.)	**Eticyclin 'Linguets'** *or* **Ovocyclin P Ampoules.** Cyclical treatment as described for primary amenorrhœa Two or three courses may establish spontaneous rhythm	To build up a normal uterus and/or encourage the establishment of regular menstruation
To replace deficiency of luteal hormone in primary and secondary amenorrhœa. (See p 88.)	**Lutocyclin 'Linguets'** 25 mg daily for 8 days starting at the end of the œstrogen course or **Lutocyclin Ampoules** 10 mg. alternate days for four injections starting at the end of the œstrogen course	The endometrium, which has proliferated under the influence of œstrogenic stimulation is converted to the progestational (decidual) state.

GROUP.	TREATMENT.	PRINCIPLE.
Essential Dysmenorrhœa. (See p. 90)	(a) **Eticyclin 'Linguets'** 0·05 mg. daily from the 5th to the 26th day of the cycle or **Ovocyclin P Ampoules** 5 mg. twice a week for five injections starting on the 5th day of the cycle.	Either to prevent ovulation or to abolish ischæmia.
	[illegible] struation.	[illegible]
	(c) **Perandren 'Linguets'** 10–15 mg daily throughout the cycle or **Perandren Ampoules** 10 mg alternate days during the premenstrual and menstrual weeks.	To relieve pelvic congestion.
Premenstrual Tension. (See p. 93)	(a) **Lutocyclin 'Linguets'** 25 mg. daily or **Lutocyclin Ampoules** 10 mg alternate days for 8 days starting 10 days before menstruation.	To counteract excess of œstrogen.
	(b) **Perandren 'Linguets'** 10 mg. daily or **Perandren Ampoules** 10 mg. alternate days during the 8 premenstrual days.	Suppression of excess of œstrogen production
Functional Uterine Bleeding. (See p. 93)	(a) **Eticyclin 'Linguets'** 0·1 mg. three times daily for 20 days and **Lutocyclin 'Linguets'** 25–50 mg. daily from the 16th to 20th day or **Ovocyclin P Ampoules** 5 mg. daily for 15 days followed by **Lutocyclin Ampoules** 5 mg. daily for 5 days.	To raise œstrogen above the threshold or bleeding level.

GROUP.	TREATMENT.	PRINCIPLE.
Functional Uterine Bleeding —*(continued)*	(b) **Lutocyclin Ampoules** 5–10 mg daily or **Lutocyclin 'Linguets'** 25–50 mg. daily for three to five days. (*Bleeding* [illegible] Re[illegible] days before each subsequent period or on the first day of bleeding.	Restoration of progesterone deficiency, transformation of the endometrium to the decidual phase and [illegible]
	(c) [illegible]	[illegible]
	(d) **Perandren Ampoules** 25 mg daily plus **Lutocyclin Ampoules** 10 mg daily for 3–5 days	
Intermenstrual Bleeding. (See p. 98.)	(a) **Lutocyclin 'Linguets'** 25 mg daily or **Lutocyclin Ampoules** 5 mg. daily, for 4 days starting 2 days before the expected date of bleeding	Preservation of the integrity of the endometrium until adequate corpus luteum function is established.
	(b) **Eticyclin 'Linguets'** 0 05 mg daily for six days starting three days before bleeding is due.	Preservation of œstrogen above the bleeding or threshold level.
[illegible]	(a) [illegible]	[illegible] pro-[illegible]iency, [illegible] of the [illegible] o the [illegible] and promotion of complete shedding of the endometrium.
	(b) **Perandren Ampoules** 25–50 mg daily or on alternate days.	Suppression of excessive œstrogen production and conversion of the endometrium to a resting stage

GROUP.	TREATMENT.	PRINCIPLE.
Essential Dysmenorrhœa. (See p. 90.)	(a) **Eticyclin 'Linguets'** 0·05 mg. daily from the 5th to the 26th day of the cycle or **Ovocyclin P Ampoules** 5 mg. twice a week for five injections starting on the 5th day of the cycle.	Either to prevent ovulation or to abolish ischæmia.
	[illegible] struation.	[illegible]
	(c) **Perandren 'Linguets'** 10–15 mg daily throughout the cycle or **Perandren Ampoules** 10 mg. alternate days during the premenstrual and menstrual weeks.	To relieve pelvic congestion.
Premenstrual Tension. (See p. 93)	(a) **Lutocyclin 'Linguets'** 25 mg. daily or **Lutocyclin Ampoules** 10 mg. alternate days for 8 days starting 10 days before menstruation.	To counteract excess of œstrogen.
	(b) **Perandren 'Linguets'** 10 mg daily or **Perandren Ampoules** 10 mg. alternate days during the 8 premenstrual days.	Suppression of excess of œstrogen production
Functional Uterine Bleeding. (See p. 93.)	(a) **Eticyclin 'Linguets'** 0·1 mg three times daily for 20 days and **Lutocyclin 'Linguets'** 25–50 mg daily from the 16th to 20th day or **Ovocyclin P Ampoules** 5 mg. daily for 15 days followed by **Lutocyclin Ampoules** 5 mg. daily for 5 days.	To raise œstrogen above the threshold or bleeding level.

GROUP.	TREATMENT.	PRINCIPLE.
Frigidity. (See p. 103)	**Perandren 'Linguets'** 10–30 mg. daily for 3–6 months or **Perandren Ampoules** 10–25 mg. two to three times weekly for 6–8 weeks. **Perandren Ointment** Inunction of clitoris daily.	Increase of sensitivity of the external genitalia and clitoris.
Excessive Libido. (See p. 103)	**Lutocyclin 'Linguets'** 25 mg daily or **Lutocyclin Ampoules** 10–20 mg. alternate days during the second half of the menstrual cycle.	Corrects the progesterone deficiency which may be present in nymphomania.
Mastopathia (Fibroadenosis, Chronic Mastitis). (See p. 104)	**Perandren Ointment** Local inunction of the breast with 2 inches twice daily.	Relief of pain by counteraction of œstrogenic effect.
Threatened Abortion due to progesterone deficiency. (See p 106.)	**Lutocyclin Ampoules** 10 mg daily until bleeding ceases, then 25 mg. twice weekly (See Depot Therapy Section.)	Preservation of integrity of the decidual endometrium and implantation of the fœtus.
Habitual Abortion due to progesterone deficiency. (See p. 106)	**Lutocyclin Ampoules** 10 mg on alternate days during the second half of the menstrual cycle and when the period is missed 25 mg. twice weekly to the 7th month or **Lutocyclin 'Linguets'** 25 mg daily starting at the beginning of the second half of the menstrual cycle and continuing if the period is missed, to the 7th month. (See Depot Therapy Section.)	Preservation of integrity of the decidual endometrium and implantation of the fœtus.
Induction of Labour, Missed Abortion, Carneous Mole, Intra-Uterine Fœtal Death. (See p. 108)	**Ovocyclin P Ampoules** 5 mg. four-hourly or **Eticyclin 'Linguets'** 0.5 mg 2-hourly up to 15 doses.	Increasing the sensitivity of the uterus to naturally secreted oxytocic substance, and to the routine treatment by oxytocic drugs and mechanical stimulants.

GROUP.	TREATMENT.	PRINCIPLE.
Sterility due to: (a) **Failure of Ovulation.** (See p. 99.)	**Eticyclin 'Linguets'** 0·01 mg. daily for three weeks with **Lutocyclin 'Linguets'** 25 mg. daily during the third week.	Stimulation of the pituitary to release gonadotrophins in order to induce ovulation
(b) **Deficient Motility of Fallopian Tubes.** (See p. 99.)	**Eticyclin 'Linguets'** 0·05 mg. alternate days for a month or **Ovocyclin P Ampoules** 5 mg. every five days for the same period.	To increase the lumen and stimulate peristaltic movements.
(c) **Progesterone Deficiency Leading to Failure of Nidation.** (See p. 99.)	**Lutocyclin Ampoules** 10 mg. on alternate days during the second half of the menstrual cycle or **Lutocyclin 'Linguets'** 25 mg. daily during the same period.	Promotion of implantation of the fertilised ovum.
Inhibition of Menstruation. (See p. 56.)	(a) **Eticyclin 'Linguets'** 0·5 mg. four times daily or **Ovocyclin P Ampoules** 10 mg. on the 1st or 2nd day after menstruation. (b) **Perandren Ampoules** 25 mg. daily or **Perandren 'Linguets'** 100 mg. daily starting three days before period is due.	To delay ovulation and thereby delay the onset of the subsequent menstrual period.
The Climacteric, (See p. 100.) **Involutional Melancholia.** (See p. 102.)	**Eticyclin 'Linguets'** 0·01–0·05 mg. daily or **Ovocyclin P Ampoules** 1 mg. once to three times weekly or 5 mg. weekly (See Depot Therapy Section.)	Compensation for the withdrawal of the internal secretion of the ovaries and restoration of normal hormonal equilibrium. After symptoms are fully under control, a progressive reduction of dosage brings about a gradual adjustment of equilibrium to a different level.
Pruritus Vulvæ, [illegible]	**Eticyclin 'Linguets'** [illegible]	Histological and func- [illegible] -nges in the [illegible] -pithelium [illegible] oestrogen- [illegible] are reversed [illegible] -ial replace- [illegible] oestrogenic [illegible]

GROUP.	TREATMENT.	PRINCIPLE.
Enuresis. (See p. 115.)	**Perandren 'Linguets'** 10–30 mg. daily for one to three months or **Perandren Ampoules** 5–10 mg daily to 25 mg twice weekly for one to three months.	Increase of the tonus of the bladder and sphincter muscles.
Acne Vulgaris. (See p. 116)	**Eticyclin 'Linguets'** 0 01–0 05 mg. daily.	Restores the androgen-œstrogen balance and counteracts androgenic effect.
Buccal Leukoplakia, Ulcerative Stomatitis, Senile Gingivitis. (See p 116)	**Eticyclin 'Linguets'** 0 01–0 05 mg. daily or **Ovocyclin P Ampoules** 1 mg on alternate days.	The integrity of the buccal mucosa appears to depend on an adequacy of œstrogen.
Atrophic Rhinitis. (See p 118.)	**Ovocyclin P Ampoule Solution** Intranasal spray twice daily with 0 5 c cm (1 mg. per c.cm. ampoule solution) after irrigation with physiological saline.	Stimulation of the secretion and vascularity of the nasal mucosa.
Hypopituitarism, Simmonds's Disease. (See p 118)	**Perandren Ampoules** [illegible]	Promotion of anabol- [illegible]
Cushing's Syndrome. (See p. 119.)	**Perandren Ampoules** 25–50 mg daily.	Promotion of anabolism of protein, causing improvement of certain clinical features. (Will cause or increase virilism)
Angina Pectoris, Thromboangiitis Obliterans, Arteriosclerosis. (See p. 120.)	(a) **Perandren 'Linguets'** 10–50 mg. daily or **Perandren Ampoules** 25 mg. once to twice weekly. (b) **Eticyclin 'Linguets'** 0·01 mg daily or **Ovocyclin P Ampoules** 5 mg. weekly.	Vasodilator effect.

GROUP.	TREATMENT.	PRINCIPLE
Suppression of Lactation, and Breast Engorgement. (See p. 108)	(a) **Eticyclin 'Linguets'** 0·1 mg 3 times daily for 3 days, then 0·05 mg 3 [illegible] daily.	Counteraction of the sudden fall in the level of œstrogen which [illegible]
	(b) **Perandren Ampoules** 25 mg once or twice daily for one to three days.	Acts presumably by inhibition of the pituitary.
Carcinoma of the Breast; inoperable and post-operative. (See p. 110.)	(a) **Perandren Ampoules** 100–200 mg. three to five times weekly or **Perandren 'Linguets'** 50 mg. three to six times daily.	Action unknown.
	(b) **Eticyclin 'Linguets' (Contraindicated in patients under 60)** 0·15–1 mg. daily or **Ovocyclin P Ampoules (Contraindicated in patients under 60)** 5–10 mg. daily.	Action unknown.
Leucorrhœa. (See p. 113.)	**Eticyclin 'Linguets'** 0·01–0·05 mg. daily or **Ovocyclin P Ampoules** 1 mg once to three times weekly or 5 mg weekly or fortnightly.	To promote adequate epithelialisation and raise local resistance.
Gonoccal Vulvo-Vaginitis in children. (See p 113)	**Eticyclin 'Linguets'** 0·01–0·05 mg daily or **Ovocyclin P Ampoules** 1 mg. weekly or fortnightly. The local application of **Ovocyclin Ointment** may be useful.	Epithelialisation of the infantile, non-epithelialised vaginal mucosa and production of an acid vaginal secretion, both of which are inimical to the growth of the gonococcus.

COMMON TO BOTH SEXES

Prematurity. (See p. 114.)	**Perandren 'Linguets'** 5 mg. daily (crushed and mixed with a feed).	Promotion of protein anabolism.

REFERENCES

REFERENCES

Adair, F. E (1949) "The Use of Irradiation, Surgery and Hormones in Breast Cancer", *Proc. R. Soc. Med*, 42, 468.

Adrian, J. (1938) "Therapeutic Value of Injections of Estrogen in Undesirable Lacteal Production", *Gynéc. et. Obstét.* 37, 178

Albert, S (1942) "Influence of Testosterone on the Morphogenetic Actions of Estradiol", *Endocrinology*, 30, 454.

Albright, F. (1938) "Metropathia Hemorrhagica", *J. Maine med. Ass.*, 29, 235.

Al[illegible] Syndrome [illegible] gluconeo- [illegible]", *J. clin.* [illegible]

Albright, F., Smith, C. H., and Fraser, R. (1942) "A Syndrome Characterised by a Primary Ovarian Insufficiency and Decreased Stature", *Amer. J med Sci*, 204, 625.

Allen, E. (1935) "Menstruation", *J. Amer. med. Ass.*, 104, 1901.

Allen, E. (1938) "Growth of Tissues in Response to Ovarian Follicular Hormone and Associated Experiments", *Les Hormones Sexuelles, II* 1. Hermann & Cie, Paris.

Allen, E, Diddle, A W, Burford, T H., and Elder, J H (1936) "Analyses of Urine of the Chimpanzee for Estrogenic Content during Various Stages of the Menstrual Cycle", *Endocrinology*, 20, 546.

Allen, E, and Doisy, E. A (1923) "An Ovarian Hormone", *J Amer. med Ass.*, 81, 819.

Allen, W. M. (1944) "Biological Activity of Various Estrogens", *South med. J*, 37, 270

Allen, W. M., Butenandt, A., Corner, G W., and Slotta, K. H (1935) "Nomenclature of Corpus Luteum Hormone", *Lancet*, 2, 454.

Annotation (1938) "Effect of Œstrin on the Basal Metabolic Rate", *Brit. med J.*, 1, 1273

Barnes, J (1942) "Inhibition of Lactation by Synthetic Œstrogenic Substances with Special Reference to Dienœstrol", *Brit med. J*, 1, 601.

Barton, M, and Wiesner, B P. (1945) "Thermogenic Effect of Progesterone", *Lancet*, 2, 671.

Beall, D (1940) "The Isolation of *a*–Œstradiol and Œstrone from Horse Testes", *Biochem J*, 34, 1293

Beaser, S. B, and Massell, T. B. (1942) "Therapeutic Evaluation of Testosterone in Peripheral Vascular Disease", *New Engl J. Med.*, 227, 43

Beilly, J. S, and Solomon, S (1940) "The Inhibition of Lactation Post-partum with Testosterone Propionate", *Endocrinology*, 26, 236.

Bender, S. (1948) "The Guterman Test in Threatened Abortion", *Brit med J.*, 1, 683.

Bender, X. (1937) "Premiers Essais de Traitement des Congestions Mammaires Douloureuses Pré-Menstruelles par le Propionate de Testostérone", *C.R Soc. Franc. Gynécol*, 7, 222

Burrill, M. W., and Greene, R. R. (1946) "Effects of Rat's Liver on Activity of Testosterone and Methyl Testosterone", *Endocrinology*, 31, 73.

Buxton, C. L., and Atkinson, W. B. (1948) "Hormonal Factors Involved in the Regulation of Basal Body Temperature during the Menstrual Cycle and Pregnancy", *J. clin Endocrinol*, 8, 544.

Callow, N. H. (1939) "The Isolation of Two Transformation Products of Testosterone from Urine", *Biochem J.*, 33, 559.

Callow, N. H., and Callow, R. K. (1939) "The Isolation of 17-Ketosteroids from the Urine of Normal Women", *Biochem. J.*, 33, 931.

Callow, N. H., and Callow, R. K. (1940) "Excretion of Androgens by Eunuchs. The Isolation of 17-Ketosteroids from the Urine", *Biochem. J.*, 34, 276.

Callow, N. H., Callow, R. K., and Emmens, C. W. (1939) "The Effect of the Administration of Testosterone Propionate on the Urinary Excretion of Compounds Allied to the Steroid Hormones", *J. Endocrinol*, 1, 99.

Callow, R. K., and Parkes, A. S. (1937) "The Chemistry and Assay of Male Hormones", *Brit. med. J*, 1, 456.

Campbell, R. E., and Hisaw, F. L. (1936) "Use of Corpus Luteum in Treatment of Dysmenorrhœa", *Amer J Obstet Gynec.*, 31, 508.

Cantor, M. M, Vant, J R, Conn, L. C., and Huston, M. J. (1942) "Sex Hormones in Obstetrics and Gynæcology", *Canad. med. Ass. J*, 47, 12.

Chase, H. C. (1947) "Breast Cancer", *Surg. Gynec & Obst.*, 85, 712.

Cohen, S L, and Marrian, G. F. (1936) "The Isolation and Identification of a Combined Form of Œstriol in Human Pregnancy Urine", *Biochem. J.*, 30, 57.

Corner, G. W. (1937) "The Hormone of the Corpus Luteum", *Tr. Edinburgh obst. Soc.*, 61

Cramer, W., and Gye, W. E (1936) "Œstrin and Cancer", *Lancet*, 2, 1365

Cramer, W., and Horning, E. S. (1936a) "Experimental Production by Œstrin of Pituitary Tumours with Hypopituitarism and of Mammary Cancer", *Lancet*, 1, 247.

Cramer, W., and Horning, E S. (1936b) "The Effect of Œstrin on the Pituitary Gland", *Lancet*, 1, 1056

Creevy, C. D., and Rea, C. E (1940) "The Treatment of Impotence by Male Sex Hormone", *Endocrinology*, 27, 392.

Crooke, A C., and Callow, R. K. (1939) "The Differential Diagnosis of Forms of Basophilism (Cushing's Syndrome) particularly by the Estimation of Urinary Androgens", *Quart. J. Med.*, 8, 233

Cutuly, E., McCullagh, D. R., and Cutuly, E. C (1937) "Effects of Androgenic Substances in Hypophysectomised Rats", *Amer. J Physiol*, 119, 121

Danziger, L. (1944) "Specific Treatment of Psychosis due to Estrogen Deficiency", *Arch. Neurol & Psychiat.*, 51, 462.

David, K, Dingemanse, E, Freud, J., and Laqueur, E. (1935) "Ueber krystallinisches männliches Hormon aus Hoden (Testosteron), wirksamer als aus Harn oder Cholesterin bereitetes Androsteron", *Hoppe-Seyl Z.*, 5/6, 281.

Berlind, M. (1943) "Contribution to Treatment of Amenorrhea", *J. clin. Endocrinol.*, 3, 457.

Berry, J. V. (1937) "Estrogenic Hormones in the Treatment of Vulvo-Vaginitis in Children", *Canad. med Ass. J.*, 36, 396.

Bickel, G. (1937) "L'Hormone Génitale Male et ses Applications Thérapeutiques", *Praxis*, 26, 755.

Bickers, W. (1944) "Menstrual Irregularity", *Virginia med. Monthly*, 71, 513.

Bickers, W. (1946) "Ethinyl Estradiol in the Treatment of Metrorrhagia", *Amer. J. Obstet. Gynec.*, 51, 100.

Birnberg, C. H., Kurzrok, L., and Klor, S. J. (1940) "Inhibition of Lactation during the Puerperium by Testosterone Propionate", *Amer. J. Obstet. Gynec.*, 39, 107.

Birnberg, C. H., Livingston, S. H., Kurzrok, L., and Sherber, D. A. (1947) "Ethinyl Estradiol", *Amer. J. Obstet. Gynec.*, 54, 855

Bishop, P. M. F. (1937a) "Hormones in the Treatment of Menstrual Disturbances", *Brit. med. J.*, 1, 763.

Bishop, P. M F. (1937b) "The Menopause", *Brit. med. J.*, 1, 819.

Bishop, P. M. F. (1938) "A Clinical Experiment in Œstrin Therapy", *Brit. med. J.*, 1, 939.

Bishop, P. M. F. (1947) "Gynæcological Endocrinology", Livingstone, Edinburgh.

Bishop, P. M. F. (1949) "The Use of Sex Hormones in Therapeutics", *Brit. med. J.*, 1, 165.

Bishop, P. M. F., and Folley, S. J. (1944) "Implantation of Testosterone in Cast Pellets", *Lancet*, 1, 434.

Biskind, G. R. (1940) "Inactivation of Methyl Testosterone in Castrate Male Rats", *Proc. Soc. exp Biol. N.Y.*, 43, 259.

Bleriot, M. (1938) "Traitement de l'Ectopie Testiculaire et de l'Insuffisance des Glandes Génitales chez l'Enfant, par le Propionate de Testostérone", *Conc. Med.*, 60, 731.

Boger, W. P. (1946) "Methyl Testosterone and Surgical Castration in the Treatment of Carcinoma of the Breast", *J. clin. Endocrinol.*, 6, 88.

Bonnell, R. W., Pritchett, C. P., and Rardin, T. E. (1941) "Treatment of Angina Pectoris and Coronary Artery Disease with Sex Hormones", *Ohio State med J*, 37, 554.

Brown, W. E, Bradbury, J. T., and Jennings, A F (1948) "Experimental Alteration of the Human Ovarian Cycle by Estrogen", *J. clin. Endocrinol.*, 8, 453

Browne, J. S. L., Henry, J. S., and Venning, E M. (1937) "The Corpus Luteum Hormone in Pregnancy", *J. clin Invest.*, 16, 678

Browne, R. Christie (1948) "The Biological Aspect in the Treatment of the Infertile Marriage", *Brit med J*, 2, 851

Burckhardt, W. (1946) "Zur Behandlung Peripherer Funktioneller Durchblutungsstörungen Insbesondere mit Sexual Hormonen", *Schweiz. med. Wschr*, 76, 1147

Burn, J. H. (1937) "Biological Standardisation", *Oxford University Press.*

Burrill, M. W., and Greene, R. R. (1946) "Effects of Rat's Liver on Activity of Testosterone and Methyl Testosterone", *Endocrinology*, 31, 73.

Buxton, C. L., and Atkinson, W. B. (1948) "Hormonal Factors Involved in the Regulation of Basal Body Temperature during the Menstrual Cycle and Pregnancy", *J. clin. Endocrinol.*, 8, 544.

Callow, N. H. (1939) "The Isolation of Two Transformation Products of Testosterone from Urine", *Biochem. J.*, 33, 559.

Callow, N. H., and Callow, R. K. (1939) "The Isolation of 17-Ketosteroids from the Urine of Normal Women", *Biochem J.*, 33, 931.

Callow, N. H., and Callow, R. K. (1940) "Excretion of Androgens by Eunuchs: The Isolation of 17-Ketosteroids from the Urine", *Biochem. J.*, 34, 276

Callow, N. H., Callow, R. K., and Emmens, C. W. (1939) "The Effect of the Administration of Testosterone Propionate on the Urinary Excretion of Compounds Allied to the Steroid Hormones", *J. Endocrinol.*, 1, 99.

Callow, R. K., and Parkes, A. S. (1937) "The Chemistry and Assay of Male Hormones", *Brit med. J.*, 1, 456.

Campbell, R. E., and Hisaw, F. L. (1936) "Use of Corpus Luteum in Treatment of Dysmenorrhœa", *Amer. J. Obstet Gynec.*, 31, 508

Cantor, M. M., Vant, J R., Conn, L C., and Huston, M J. (1942) "Sex Hormones in Obstetrics and Gynæcology", *Canad. med Ass. J.*, 47, 12.

Chase, H. C. (1947) "Breast Cancer", *Surg. Gynec. & Obst*, 85, 712.

Cohen, S. L., and Marrian, G F (1936) "The Isolation and Identification of a Combined Form of Œstriol in Human Pregnancy Urine", *Biochem. J.*, 30, 57.

Corner, G W. (1937) "The Hormone of the Corpus Luteum", *Tr Edinburgh obst Soc*, 61.

Cramer, W., and Gye, W E. (1936) "Œstrin and Cancer", *Lancet*, 2, 1365.

Cramer, W., and Horning, E S. (1936a) "Experimental Production by Œstrin of Pituitary Tumours with Hypopituitarism and of Mammary Cancer", *Lancet*, 1, 247.

Cramer, W., and Horning, E. S (1936b) "The Effect of Œstrin on the Pituitary Gland", *Lancet*, 1, 1056

Creevy, C D., and Rea, C E (1940) "The Treatment of Impotence by Male Sex Hormone", *Endocrinology*, 27, 392

Crooke, A. C., and Callow, R K. (1939) "The Differential Diagnosis of Forms of Basophilism (Cushing's Syndrome) particularly by the Estimation of Urinary Androgens", *Quart J. Med*, 8, 233

Cutuly, E, McCullagh, D. R, and Cutuly, E C. (1937) "Effects of Androgenic Substances in Hypophysectomised Rats", *Amer. J Physiol*, 119, 121.

Danziger, L. (1944) "Specific Treatment of Psychosis due to Estrogen Deficiency", *Arch. Neurol & Psychiat*, 51, 462

David, K., Dingemanse, E, Freud, J, and Laqueur, E (1935) "Ueber krystallinisches männliches Hormon aus Hoden (Testosteron), wirksamer als aus Harn oder Cholesterin bereitetes Androsteron", *Hoppe-Seyl Z.*, 5/6, 281

David, K., Freud, J, and de Jongh, S. E. (1934) "Conditions of Hypertrophy of Seminal Vesicles in Rats: (ii) The Effect of Derivatives of Œstrone (Menformon)", *Biochem. J.*, 28, 1360.

Davis, M. E, and Fugo, N. W. (1948) "The Cause of Physiologic Basal Temperature Changes in Women", *J. clin. Endocrinol.*, 8, 550.

Day, R. V., Martin, H. W., Kutzmann, A. A., and Kessler, E. E. (1938) "Sex Hormone Therapy for Prostatism", *Amer. J. Surg.*, 1, 100

Deanesly, R., and Parkes, A. S. (1937a) "Multiple Activities of Androgenic Compounds", *Quart. J. exp. Physiol.*, 26, 393.

Deanesly, R., and Parkes, A. S. (1937b) "Factors Influencing the Effectiveness of Administered Hormones", *Proc. R. Soc. s. B*, 124, 279

Deanesly, R., and Parkes, A. S (1938) "Further Experiments on Administration of Hormones by Subcutaneous Implantation of Tablets", *Lancet*, 2, 606.

Deanesly, R, and Parkes, A. S. (1943) "Deposition of Protein Material in Implanted Pellets of Steroid Hormones", *Lancet*, 2, 500.

Desmarest and Capitain (1937a) "Le Traitement des Mastopathies par l'Acétate de Testostérone", *Pr. méd.*, 45, 777.

Desmarest and Capitain (1937b) "Mastopathies et Acétate de Testostérone", *Pr méd.*, 45, 1109

Dingemanse, E, Laqueur, E., and Mühlbock, O. (1938) "Chemical Identification of Œstrone in Human Male Urine", *Nature*, 141, 927

Discussion on Advanced Cases of Carcinoma of the Breast Treated by Stilbœstrol (1944), *Proc R. Soc. Med.*, 37, 731.

Donald, H. R. (1938) "The Female Climacteric and the Menopause", *Brit. med J*, 1, 727

Dorfman, R. I. (1940) "Fate of Testosterone in the Human", *Proc. Soc exp Biol. N.Y.*, 45, 739

Dorfman, R. I. (1941) "Etioallocholanol-3 (β)-17-One (Isoandrosterone) as a Metabolite of Testosterone in the Human Male", *Proc. Soc exp. Biol. N.Y.*, 46, 351.

Dunn, C. W (1946) "The Constitutional Effects of Male Hormone Therapy", *Clinics*, 5, 898.

Dynes, J. B. (1939) "Estrogenic Therapy of Involutional Melancholia", *Arch. Neurol. & Psychiat*, 42, 248.

Eagle, W. W., Baker, R. D., and Hamblen, E. C (1939) "Atrophic Rhinitis Treatment with Estrogenic Substances with Biopsy Before and After Treatment", *Arch. Otolaryng.*, 30, 319

Edwards, E. A., Hamilton, J B, and Duntley, S Q (1939) "Testosterone Propionate as a therapeutic agent in Patients with Organic Disease of the Peripheral Vessels, Preliminary Report", *New Engl. J. Med*, 220, 865.

Egger, K (1944) "Zur Frage der Hormonalen Beeinflussbarkeit Des Miktionsvorganges Beim Prostatiker", *Schweiz. med. Wschr*, 74, 676.

Eidelsberg, J., and Ornstein, E. A. (1940) "Observations on the Continued Use of Male Sex Hormone over Long Periods of Time", *Endocrinology*, 26, 46.

Ellison, E. T., and Burch, J. C. (1936) "The Effect of Estrogenic Substances upon the Pituitary, Adrenals and Ovaries", *Endocrinology*, 20, 746.

Emmens, C W. (1941) "Rate of Absorption of Androgens and Estrogens in Free and Esterified form from Subcutaneously Implanted Tablets", *Endocrinology*, 28, 633.

Emmens, C. W , and Bradshaw, T. E. T. (1939) "Mutual Antagonism between Œstrogens and Androgens", *J. Endocrinol* , 1, 378.

[illegible]

Falls, F H., Lackner, J. E , and Krohn, L. (1936) "Effect of Progestin and Estrogenic Substances on Human Uterine Contractions", *J. Amer. med Ass* , 106, 4, 271.

Farrow, J. H., and Woodard, H Q (1942) "The Influence of Androgenic and Estrogenic Substance on the Serum Calcium in Cases of Skeletal Metastases from Mammary Cancer", *J. Amer. med Ass* , 118, 339.

Fels, E (1944) "Treatment of Breast Cancer with Testosterone Propionate", *J. clin. Endocrinol* , 4, 121.

Fergusson, J D. (1946) "Carcinoma of Prostate Treated with Œstrogens", *Lancet*, 2, 551.

Finkler, R. S. (1944) "Zondek's Simplified Treatment of Secondary Amenorrhœa", *Amer. J. Obstet. Gynec* , 48, 26.

Finkler, R. S (1947) "Male Hypogonadism Treated by Sublingual Methyltestosterone", *J. clin. Endocrinol* , 7, 293.

Fisher, R. B , Krohn, P. L , and Zuckerman, S (1936) "The Occurrence of Œstrogenic Substance in the Sexual Skin of Monkeys", *Biochem J* , 30, 2219.

Folley, S J. (1936) "The Effect of Œstrogenic Hormones on Lactation and on the Phosphatase of the Blood and Milk of the Lactating Cow", *Biochem J* , 30, 2262.

Folley, S. J. (1942) "Ghost Formation in Subcutaneously Implanted Tablets of Synthetic Œstrogens", *Nature*, 150, 403.

Folley, S. J., and Malpress, F H. (1941) "Bovine Sterility The Use of Œstrogens for the Induction of Œstrus in Anœstrous Cattle", *Vet. Rec* , 53, 551.

Folley, S J , Watson, H. M S , and Bottomley, A. C. (1941) "Studies on Experimental Teat and Mammary Development and Lactation in the Goat", *J Dairy Res.*, 12, 241

Foss, G L. (1937a) "Temporary Postponement of Menstruation by Œstradiol Benzoate", *Brit. med J.*, 2, 10

Foss, G. L. (1937b) "Effect of Testosterone Propionate on a Post-Puberal Eunuch", *Lancet*, 2, 1307

Foss, G L. (1938a) "Action of Testosterone Propionate on the Female", *Lancet*, 1, 992.

Foss, G L (1938b) "Percutaneous Absorption of Male Hormone", *Lancet*, 2, 1284

Foss, G L (1939) "The Oral Application of Methyl Testosterone and its simplification of Androgen Therapy", *Brit med J.*, 2, 11

Foss, G. L., and Phillips, P. (1938) "The Suppression of Lactation by Oral Œstrogen Therapy", *Brit. med. J.*, 2, 887.

Geist, S. H., Walter, R. I., and Salmon, U. J. (1940) "Local Tissue Reaction to the Implantation of Crystals and Pellets of Estrogenic Hormone", *Proc. Soc. exp. Biol. N.Y.*, 43, 712.

Gershenfeld, D. B., and Perlmutter, I. K. (1948) "Suppression of Lactation with Ethinyl Estradiol", *J. clin. Endocrinol.*, 8, 875.

Goldman, S. F., and Markham, M. J. (1942) "Clinical Use of Testosterone in the Male Climacteric", *J. clin. Endocrinol.*, 2, 237.

Goldschmidt, E., and Streber, I. (1937) "Der Einfluss von synthetischem Testosteron-Propionat 'Perandren' auf die Testes und die sekundären Geschlechtsmerkmale infantiler männlicher Ratten", *Klin. Wschr.*, 16, 28, 993.

Greenblatt, R. B. (1943a) "Testosterone Propionate Pellet Implantation in Gynecic Disorders", *J Amer. med. Ass.*, 121, 17.

Greenblatt, R. B. (1943b) "Hormone Factors in Libido", (Editorial) *J. clin. Endocrinol.*, 3, 305.

Greenblatt, R. B. (1945) "Office Endocrinology", Thomas, Springfield, Illinois, 228.

Greenblatt, R. B., and Hair, Q (1942) "Testosterone Propionate Pellet Absorption in the Female", *J. clin. Endocrinol.*, 2, 315.

Greenblatt, R B., and Kupperman, H. S. (1946) "Further Studies on the Control of Menorrhagia", *J. clin. Endocrinol*, 6, 675.

Greenblatt, R. B , Mortara, F., and Torpin, R. (1942) "Sexual Libido in the Female", *Amer J Obstet. Gynec*, 44, 658.

Greene, R. (1941) "Endocrinology", *Practitioner*, 147, 642.

Greene, R. (1949) "Androgens", *Practitioner*, 162, 512.

Greene, R , and Robson, J. M. (1948) "The Practice of Endocrinology", Edited by Raymond Greene Eyre and Spottiswoode, London.

Greene, R. R , and Burrill, M W. (1938) "The Experimental Production of Intersexuality in the Rat", *Proc. Amer. physiol. Soc*, March/April, p. 82

Greene, R. R , and Burrill, M. W. (1941) "Effects of Large Amounts of Androgen on the Testes of the Prepuberal Rat", *Endocrinology*, 29, 64.

Greene, R R , Burrill, M. W., and Ivy, A. C (1939) "Progesterone is Androgenic", *Endocrinology*, 24, 351.

Greene, R. R., Burrill, M W , and Thomson, D. M (1940) "Further Studies on the Androgenicity of Progesterone", *Endocrinology*, 27, 469

Greene, R. R., and Wigodsky, H. S. (1938) "Effect of Local Application of Testosterone in an Ointment on Growth of Penis in the Rat", *Proc. Soc exp. Biol. N Y.*, 39, 307.

Greenhill, J. P., and Freed, S. C (1939) "Testosterone Propionate in the Treatment of Gynecological Disorders", *West. J. Surg.*, 47, 301

Greulich, W. W. (1946) "The Reliability of 'Basal' Body Temperature Changes as an Index of Ovulation in Women", *Tr. Amer. Soc Study Sterility*, p. 76.

Grignon, C. E. (1938) "Ectopie Testiculaire guérie par Opothérapie Orchitique (Propionate de Testostérone ou Perandren)", *Union méd du Canada*, 67, 90

Guterman, H. S (1944) "A Human Pregnancy Test Based upon a Color Reaction of Pregnanediol in the Urine", *J. clin. Endocrinol*, 4, 262.

Gutman, A. B, and Gutman, E. B. (1938) "An 'Acid' Phosphatase occurring in the Serum of Patients with Metastasizing Carcinoma of the Prostate Gland", *J clin Invest*, 17, 473

Haddow, A, Watkinson, J. M, Paterson, E., and Koller, P. C. (1944) "Influence of Synthetic Œstrogens upon Advanced Malignant Disease", *Brit. med. J*, 2, 393.

Hain, A. M., and Robertson, E M. (1939) "Pregnanediol Excretion in the Menstrual Cycle", *Brit. med J*, 1, 1226.

Halbrecht, I. (1945) "Ovarian Function and Body Temperature", *Lancet*, 2, 668.

Halbrecht, J. (1947) "Further Observations on the Basal Temperature in Sterile Women", *J. Obst. & Gynæc. Brit. Emp.*, 54, 848.

Hall, G. J. (1949) "The Buccal Administration of Estradiol", *J clin. Endocrinol*, 9, 382

Hall, B. V., and Lewis, R M (1936) "The Induction of an Acid Vaginal Secretion in the Immature Macaque by Injections of Œstrin", *Endocrinology*, 20, 210.

Hall, I S, and MacLeod, I A M. (1942) "Atrophic Rhinitis—The Treatment of Atrophic Rhinitis by Œstrogenic Compounds", *J Laryng. & Otol*, 57, 337.

Hamblen, E C., and Cuyler, W K (1939) "Androgens and the 'Coloring' of Women", *J Amer med Ass.*, 113, 38.

Hamblen, E. C., Cuyler, W. K., Pattee, C J, and Axelson, G. J. (1941) "Endocrine Therapy of Functional Menometrorrhagia and Ovarian Sterility", *J. clin. Endocrinol.*, 1, 221

Hamilton, J. B (1936) "Endocrine Control of the Scrotum and 'Sexual Skin' in the Male Rat", *Proc Soc exp Biol N.Y.*, 35, 386.

Hamilton, J B. (1937a) "Induction of Penile Erection by Male Hormone Substances", *Endocrinology*, 21, 774

Hamilton, J. B. (1937b) "Production of Testicular Descent in Monkeys by Male Hormone Substances", *Amer J Physiol.*, 119, 2, 325.

Hamilton, J B (1937c) "Changes in Nasal Mucosa of Monkeys (Macaca Rhesi) and Humans by Male Hormone Substances", *Proc. Soc. exp Biol N Y*, 37, 366

Hamilton, J. B. (1937d) "Treatment of Sexual Underdevelopment with Synthetic Male Hormone Substance", *Endocrinology*, 21, 649

Hamilton, J. B (1938a) "Precocious Masculine Behaviour following Administration of Synthetic Male Hormone Substance", *Proc Amer physiol Soc.*, March/April, p 88.

Hamilton, J B (1938b) "The Effect of Male Hormone upon the Descent of the Testes", *Anat. Rec*, 5, 533

Hamilton, J B (1939) "Significance of Sex Hormone in Tanning of the skin of Women", *Proc Soc exp Biol. N.Y.*, 40, 502.

Hamilton, J. B. (1941) "Male Hormone Substance: A Prime Factor in Acne", *J. clin. Endocrinol*, 1, 570.

Hamilton, J. B., and Gardner, W. U. (1937) "Effects in Female Young born of Pregnant Rats injected with Androgens", *Proc. Soc. exp. Biol. N.Y.*, 37, 570.

Hamilton, J. B., and Gilbert, J. (1938a) "Photographic Nature of Tanning of Human Skin as Shown by Studies of Male Hormone Therapy", *Science*, 88, 481.

Hamilton, J. B., and Gilbert, J. (1938b) "New Conception of Etiological Factors in the Production of Symptoms Observed in Benign Prostatic Hypertrophy: Mechanism of Control by Male Hormone Substance", *Tr. West. Sect. Am. urol. A.*, p. 144.

Hamilton, J. B., and Leonard, S. L. (1938) "The Effect of Male Hormone Substance upon the Testes and upon Spermatogenesis", *Anat. Rec.*, 71, 105.

Hamilton, J. B., and Wolfe, J. M. (1938) "The Effect of Synthetic Androgen upon the Gonadotrophic Potency of the Anterior Pituitary", *Endocrinology*, 23, 360.

Hamm, L. (1942) "Testosterone Propionate in the Treatment of Angina Pectoris", *J. clin. Endocrinol.*, 2, 325.

Harding, F. E. (1943) "Treatment of Cryptorchidism: Report on Treatment of 38 Cases with Chorionic and Pituitary Gonadotrophin and Testosterone", *J. Pediat.*, 23, 451

Harding, F. E. (1944) "Oral Substitution Therapy with Ethinyl Estradiol and Alpha-Estradiol", *Amer. J. Obstet. Gynec.*, 48, 181.

Harding, F. E. (1948) "Sublingual Methyl Testosterone for Boyhood Emotional and Genital Immaturity", *J. Pediat.*, 32, 351.

Häussler, E. P. (1934) "Ueber das Vorkommen von α-Follikelhormon (3-Oxy-17-keto-1, 3, 5-oestratriën) im Hengsturin", *Helvet. chim. Acta*, 17, 531.

Hawkinson, L. F. (1938) "The Menopausal Syndrome. One Thousand Consecutive Patients treated with Estrogen", *J. Amer. med. Ass.*, 111, 390.

Heckel, G. P. (1938) "Inhibition of Parturition in the Rabbit by the Injection of Estrogenic Hormone", *Proc. Amer. physiol. Soc.*, March/April, p. 95.

Heckel, N. J. (1940) "The Influence of Testosterone Propionate upon Benign Prostatic Hypertrophy and Spermatogenesis. A Clinical and Pathological Study in the Human", *J. Urol.*, 43, 286.

Heckel, N. J. (1944) "Evaluation of Sex Hormones in the Treatment of Benign Prostatic Hypertrophy, Carcinoma of the Prostate and Other Diseases of the Genito-Urinary System", *J. clin. Endocrinol.*, 4, 166.

Heller, C. G., and Myers, G. B. (1944) "The Male Climacteric: its Symptomatology, Diagnosis and Treatment", *J. Amer. med. Ass.*, 126, 477.

Heller, C. G., and Nelson, W. O. (1948) "Classification of Male Hypogonadism and a Discussion of the Pathologic Physiology, Diagnosis and Treatment", *J. clin. Endocrinol.*, 8, 345.

Henry, J. S., and Browne, J. S. L. (1943) "The Contractions of the Human Uterus during the Menstrual Cycle. The Effect of Progesterone and Posterior Pituitary Extract upon the Motility of the Human Uterus", *Amer. J. Obstet. Gynec.*, 45, 927.

Herrmann, J. B., and Adair, F. E. (1946) "The Effect of Testosterone Propionate on Carcinoma of the Female Breast with Soft Tissue Metastases", *J. clin. Endocrinol.*, 6, 769.

Herrmann, J. B., Adair, F. E., and Woodard, H. Q. (1947) "Effect of Estrogenic Hormone on Advanced Carcinoma of the Female Breast", *Arch. Surg.*, 54, 1.

Herrmann, J. B., Kirsten, E., and Krakauer, J. S. (1949) "Hypercalcemic Syndrome Associated with Androgenic and Estrogenic Therapy", *J. clin. Endocrinol.*, 9, 1.

Hertz, R., and Meyer, R. K. (1937) "Effect of Testosterone, Testosterone Propionate and Dehydroandrosterone on Secretion of Gonadotropic Complex as Evidenced in Parabiotic Rats", *Endocrinology*, 21, 756

Hertz, R., Meyer, R. K., and Spielman, M.A. (1937) "The Specificity of Progesterone in Inducing Sexual Receptivity in the Ovariectomised Guinea Pig", *Endocrinology*, 21, 533

Hill, R. T. (1937) "Ovaries Secrete Male Hormone", I and III, *Endocrinology*, 21, 495 and 633

Hirschmann, H. (1939) "Androgens from the Urine of Ovariectomised Women", *J. biol. Chem.*, 130, 421.

Hisaw, F. L. (1938) "Hormones Regulating the Development of the Female Reproductive Tract of Macacus Rhesus Monkeys", *Les Hormones Sexuelles*, II, 55, Hermann & Cie., Paris.

Hoberman, H. D., Sims, E. A. H., and Engstrom, W. W. (1948) "The Effect of Methyltestosterone on the Rate of Synthesis of Creatine", *J. biol. Chem.*, 173, 111.

Hohlweg, W., and Inhoffen, H. H. (1939) "Pregneninolon, ein neues per os wirksames Corpus luteum-Hormon-präparat", *Klin. Wschr.*, 18, 77.

Hotchkiss, R. S. (1944) "Effects of Massive Doses of Testosterone Propionate upon Spermatogenesis", *J. clin. Endocrinol.*, 4, 117.

Huggins, C., and Hodges, C. V. (1941) "Studies on Prostatic Cancer; effect of Castration, of Estrogen and of Androgen injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate", *Cancer Research*, 1, 293

Huggins, C., and McDonald, D. F. (1945) "Chronic Hemospermia; Its Origin and Treatment with Estrogen", *J. clin. Endocrinol.*, 5, 226

Huggins, C., Scott, W. W., and Hodges, C. V. (1941) "Studies on Prostatic Cancer, Effects of Fever, of Desoxycorticosterone and of Estrogen on Clinical Patients with Metastatic Carcinoma of Prostate", *J. Urol.*, 46, 997.

Huggins, C., Stevens, R. E. Jr., and Hodges, C. V. (1941) "Studies on Prostatic Cancer; Effects of Castration on Advanced Carcinoma of Prostate Gland", *Arch. Surg.*, 43, 209

Huhner, M. (1939) "Impotence in the Male", *Med. Rec.*, 149, 367.

Inhoffen, H. H., and Hohlweg, W. (1938) "Neue per os wirksame weibliche Keimdrusenhormon Derivate", *Naturwissenschaften*, 26, 96.

Jeffcoate, T. N. A. (1937) "The Hormone Treatment of some Disorders of Pregnancy", *Brit. med. J.*, 1, 674

Jeffcoate, T. N. A. (1940) "Missed Abortion and Missed Labour", *Lancet*, 1, 1045.

Jeffcoate, T. N. A., Lister, U. M., Hargreaves, B., and Roberts, H. (1948) "Ethinyl Oestradiol", *Brit. med. J.*, 2, 809

Joël, C. A. (1942) "Clinical Results Obtained with Sublingual Administration of Methyl Testosterone", *J. clin. Endocrinol*, 2, 116.

Jones, M. S., MacGregor, T. N., and Tod, H. (1937) "Effect of Estradiol Benzoate on Depressions at the Menopause", *J. Amer. med. Ass*, 109, 1788.

Karnaky, K. (1940) "Endocrines in Gynecology and Obstetrics with Special Reference to Stilbestrol in Treatment of Uterine Bleeding", *Texas State J. Med.*, 36, 379

Kaufmann, C. (1933) "Echte Menstruation bei einer kastrierten Frau durch Zufuhr von Ovarialhormonen", *Zbl. Gynak.*, 57, 42.

Kaufmann, C. (1937) "Clinical Uses of the Female Sex Hormone", *J. Obst. & Gynec.*, 44, 310.

Kearns, W. M. (1942) "Treatment of Carcinoma of Prostate with Estrogens", *Wisconsin med. J.*, 41, 575.

Kenyon, A T. (1938) "The Effect of Testosterone Propionate on the Genitalia, Prostate, Secondary Sex Characters, and Body Weight in Eunuchoidism", *Endocrinology*, 23, 121.

Kenyon, A. T., Knowlton, K., and Sandiford, I. (1944) "The Anabolic Effects of the Androgens and Somatic Growth in Man", *Ann. intern. Med.*, 20, 632.

Kenyon, A. T., Sandiford, I, Bryan, A H., Knowlton, K., and Koch, F C. (1938) "The Effect of Testosterone Propionate on Nitrogen, Electrolyte, Water and Energy Metabolism in Eunuchoidism", *Endocrinology*, 23, 135.

Kinsell, L W (1947) "Spermatogenesis in a 'pan-hypopituitary' eunuchoid, as the results of testosterone therapy", *J clin Endocrinol.*, 7, 781.

Klaften, E (1937) "Hormonal Regulation of Biologic Phenomena in the Vagina", *Wien klin. Wschr.*, 49, 1560

Klein, F. (1938) "Zur Frage des Climacterium Virile", *Med. Klin*, 7, 244

Klein, M, and Parkes, A S (1936) "Progesterone-like Activity of Certain Male Hormone Compounds", *J Soc chem. Indust.*, 55, 236.

Klein, M., and Parkes, A S. (1937) "The Progesterone-like Action of Testosterone and Certain Related Compounds", *Proc. R. Soc. s. B*, 121, 574

Klinefelter, H. F Jr., Reifenstein, E C Jr, and Albright, F (1942) "Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism and Increased Excretion of Follicle-Stimulating Hormone", *J clin Endocrinol*, 2, 615.

Knaus, H. (1929) "Eine neue Methode zur Bestimmung des Ovulationstermines", *Zbl Gynak*, 53, 2193

Knaus, H. (1930) "Zur Frage der Standardisation des Corpus-Luteum-Extraktes", *Arch. f. exper. Path. u. Pharmakol.*

Knowlton, K., Kenyon, A. T., Sandiford, I., Lotwin, G., and Fricker, R. (1942) "Comparative Study of Metabolic Effects of Estradiol Benzoate and Testosterone Propionate in Man", *J. clin. Endocrinol.*, 2, 671.

Koch, F. C. (1937) "Urinary Excretion of Androgenic and Estrogenic Substances in certain Endocrine States. Studies in Hypogonadism, Gynecomastia, and Virilism", *Ann. intern. Med.*, 11, 297.

Kochakian, C. D. (1937a) "Excretion of Male Hormones", *Endocrinology*, 21, 60

Kochakian, C. D. (1937b) "Testosterone and Testosterone Acetate and the Protein and Energy Metabolism of Castrate Dogs", *Endocrinology*, 21, 750

Korenchevsky, V. (1938) Review of Annual Report of Lister Institute, *Brit. med. J.*, 1, 1379

Korenchevsky, V., and Dennison, M. (1936) "The Assay of Transdehydroandrosterone and its Effects on Male and Female Gonadectomised Rats", *Biochem. J.*, 30, 1514

Korenchevsky, V., and Dennison, M. (1937) "The Co-operative Activity of Testosterone Propionate with $\triangle^5$-Androstenediol and with Oestradiol in Male Rats", *Biochem. J.*, 31, 862

Korenchevsky, V., Dennison, M., and Brovsin, I. (1936) "The Assay and Effect of Testosterone on Rats Compared with Those of Other Sexual Hormones", *Biochem. J.*, 30, 558

Korenchevsky, V., Dennison, M., and Eldridge, M. (1937a) "The Effects of $\triangle^4$-Androstenedione and $\triangle^5$-Androstenediol on Castrated and Ovariectomized Rats", *Biochem. J.*, 31, 467

Korenchevsky, V., Dennison, M., and Eldridge, M. (1937b) "The Prolonged Treatment of Castrated and Ovariectomised Rats with Testosterone Propionate", *Biochem. J.*, 31, 475

Korenchevsky, V., Dennison, M., and Hall, K. (1937a) "The Action of Testosterone Propionate on Normal Adult Female Rats", *Biochem. J.*, 31, 780

Korenchevsky, V., Dennison, M., and Hall, K. (1937b) "The Effects of Testosterone and Testosterone Propionate on Adult Male Rats (Compared with Those on Female Rats)", *Biochem. J.*, 31, 1434

Korenchevsky, V., Dennison, M., and Simpson, S. L. (1935) "The Prolonged Treatment of Male and Female Rats with Androsterone and its Derivatives, Alone or Together with Œstrone", *Biochem. J.*, 29, 2534.

[illegible]

Krohn, L., Lackner, J. E., and Soskin, S. (1937) "Effect of Ovarian Hormones on the Human (Non-puerperal) Uterus", *Amer. J. Obstet. Gynec.*, 34, 379

Kugelmass, I. N. (1946) "Androgenic Arrest of Familial Enuresis in 75 Children", *J. clin. Endocrinol.*, 6, 823.

Kurzrok, R. (1941) "Functional Uterine Bleeding", *J. clin. Endocrinol.*, 1, 199.

Kurzrok, R., and O'Connel, C. P. (1938) "The Inhibition of Lactation during the Puerperium by Testosterone Propionate", *Endocrinology*, 23, 476.

Kushner, J. I. (1942) "Inhibition of Lactation—II Oral use of Methyl Testosterone", *J. clin. Endocrinol.*, 2, 345.

Lancaster, A. H. (1939) "Estrogenic Hormone Therapy in Sunlight Eruptions of the Female", *South. med. J.*, 32, 495

Laqueur, E., Dingemanse, E., Hart, P. C., and de Jongh, S. E. (1927) "Ueber das Vorkommen weiblichen Sexualhormons (Menformon) in Harn von Männern", *Klin. Wschr.*, 6, 1859.

Laqueur, G. L., and Fluhmann, C. F. (1942) "Action of Testosterone on the Female Rat Hypophysis", *Endocrinology*, 31, 300

Laroche, G., Marsan, F., Bompard, E., and Corcos, A. (1937) "L'Hypertrophie de la Prostate. Essais de Traitement hormonal par les Sels de Testostérone", *Pr. méd.*, 50, 932.

Lawrence, C. H., and Werthessen, N. T. (1942) "Treatment of Acne with Orally administered Estrogens", *J. clin. Endocrinol.*, 2, 636.

Lesser, M. A. (1943) "Treatment of Angina Pectoris with Testosterone Propionate; further observations", *New Engl. J. Med.*, 228, 185.

Lesser, M. A. (1946) "Testosterone Propionate Therapy in One Hundred Cases of Angina Pectoris", *J. clin. Endocrinol.*, 6, 549.

Levine, E. B., and Sellers, A. L. (1946) "Testosterone in Angina Pectoris", *Amer. J. med. Sci.*, 212, 7.

Lewis, R. M., and Adler, E. L. (1936) "Gonorrheal Vaginitis in Children", *Am J. Surg.*, 3, 529.

Lisser, H., and Curtis, L. E. (1943) "Testosterone Therapy in Male Eunuchoids IV. Results from Methyl Testosterone Linguets", *J. clin Endocrinol.*, 3, 389.

Loeser, A. (1937) "Resorption and Action of Follicular Hormone Rubbed into the Skin", *J. Obst. & Gynæc.*, 44, 710.

Loeser, A. (1938a) "The Action of Testosterone Propionate on the Uterus and Breast", *Lancet*, 1, 373.

Loeser, A. A. (1938b) "Hormone Therapy in Mastitis and Breast Cancer", *Brit. med J.*, 2, 319

Loeser, A. A. (1940) "Subcutaneous Implantation of Female and Male Hormone in Tablet Form in Women", *Brit med. J.*, 1, 479

Loeser, A. A. (1941) "Mammary Carcinoma. Response to Implantation of Male Hormone and Progesterone", *Lancet*, 2, 698.

Lyon, R. A. (1943) "Relief of Essential Dysmenorrhea with Ethinyl Estradiol", *Surg Gynec & Obst.*, 77, 657.

Lyon, R. A. (1944) "Management of the Climacteric with Ethinyl Estradiol", *Amer J. Obstet. Gynec.*, 47, 532

MacBryde, C. M. (1939) "The Production of Breast Growth in the Human Female", *J. Amer med. Ass.*, 112, 1045.

MacGregor, T. N. (1938a) "Œstradiol Benzoate in Senile Vaginitis", *Lancet*, 2, 22.

MacGregor, T. N. (1938b) "Dysfunctional Uterine Bleeding treated with Progesterone", *Brit. med J*, 2, 116

Marrian, G F. (1929) "The Chemistry of Œstrin", *Biochem. J*, 23, 1090.

Marrian, G. F., and Butler, G. C. (1937) "The Hormones", *Ann. Rev. Biochem.*, 6, 303.

Martin, P. L. (1943) "Detection of Ovulation by Basal Temperature Curve with correlating Endometrial Studies", *Amer. J. Obstet Gynec*, 46, 53.

Mason, H. L (1948) "Steroid Nomenclature", *J. clin Endocrinol*, 8, 190.

Mason, H. L., and Kepler, E. J. (1945) "Isolation of Steroids from Urine of Patients with Adrenal Cortical Tumors and Adrenal Cortical Hyperplasia· New 17-ketosteroid androstane-3(*a*) 11-diol-17-one", *J. biol. Chem*, 161, 235.

Masson, G. (1945) "Spermatogenic Activity of Various Steroids", *Amer J med Sci.*, 209, 324

McCormack, G (1946) "A Comparison of the Color Chemical Test with the Friedman Modications of the Ascheim-Zondeck Test", *Amer. J. Obstet. Gynec*, 51, 722

McCrea, L. E (1946) "Carcinoma of the Prostate A Resumé of Treatment with Ethinyl Œstradiol, Preliminary Report", *J. Urol.*, 56, 697.

McCullagh, E P. (1939) "Treatment of Testicular Deficiency with Testosterone Propionate", *J. Amer. med Ass*, 112, 1037

McCullagh, E. P, and Hruby, F. J. (1949) "Testis-Pituitary Interrelationship. The Relative Inability of Testosterone to Reduce Urinary Gonadotropin in Eunuchoid Men", *J. clin Endocrinol*, 9, 113.

McCullagh, E. P., and McGurl, F J. (1940) "Effects of Testosterone Propionate on Epiphyseal Closure, Sodium and Chloride Balance and on Sperm Counts", *Endocrinology*, 26, 377

McEuen, C. S., Selye, H., and Collip, J. B. (1936) "Some Effects of Prolonged Administration of Œstrin in Rats", *Lancet*, 1, 775.

McEuen, C. S., Selye, H, and Collip, J. B (1937) "Effects of Testosterone on Somatic Growth", *Proc. Soc. exp Biol N.Y.*, 36, 307.

McGinn, E. J. (1942) "Functional Uterine Bleeding", *J clin. Endocrinol.*, 2, 302

McGrath, E (1935) "Experimental Peripheral Gangrene", *J. Amer. med Ass*, 105, 854

McGrath, E. J, and Herrmann, L. G. (1944) "Influence of Œstrogens on Peripheral Vasomotor Mechanism", *Ann Surg.*, 120, 607.

McLellan, A. (1940) "Response of Non-gravid human uterus to Posterior-Pituitary Extract and its fractions Oxytocin and Vasopressin" *Lancet*, 1, 919.

Meek, B. E, and Murby, W. H. (1944) "Œstrogens for Prevention of Post-Partum Breast Engorgement", *Canad med Ass. J*, 50, 241

Meyer, R. K, and Hertz, R (1937) "Effect of Œstrone on Secretion of Gonadotropic Complex as Evidenced in Parabiotic Rats", *Amer. J. Physiol*, 120, 232.

Miescher, K. (1944) "Ueber Steroide, Konstitution und Synthese Hochwirksame Abkömmlinge œstrogener Hormone", *Helvet. chim. Acta*, 27, 1727.

Kurzrok, R. (1941) "Functional Uterine Bleeding", *J. clin. Endocrinol.*, 1, 199.

Kurzrok, R., and O'Connel, C. P. (1938) "The Inhibition of Lactation during the Puerperium by Testosterone Propionate", *Endocrinology*, 23, 476.

Kushner, J. I. (1942) "Inhibition of Lactation—II Oral use of Methyl Testosterone", *J. clin. Endocrinol.*, 2, 345.

Lancaster, A. H. (1939) "Estrogenic Hormone Therapy in Sunlight Eruptions of the Female", *South. med. J.*, 32, 495.

Laqueur, E., Dingemanse, E., Hart, P. C., and de Jongh, S. E. (1927) "Ueber das Vorkommen weiblichen Sexualhormons (Menformon) in Harn von Mannern", *Klin. Wschr.*, 6, 1859.

Laqueur, G. L., and Fluhmann, C. F. (1942) "Action of Testosterone on the Female Rat Hypophysis", *Endocrinology*, 31, 300.

Laroche, G., Marsan, F., Bompard, E., and Corcos, A. (1937) "L'Hypertrophie de la Prostate. Essais de Traitement hormonal par les Sels de Testostérone", *Pr. méd.*, 50, 932.

Lawrence, C. H., and Werthessen, N. T. (1942) "Treatment of Acne with Orally administered Estrogens", *J. clin. Endocrinol.*, 2, 636

Lesser, M. A. (1943) "Treatment of Angina Pectoris with Testosterone Propionate; further observations", *New Engl. J. Med.*, 228, 185.

Lesser, M. A. (1946) "Testosterone Propionate Therapy in One Hundred Cases of Angina Pectoris", *J. clin. Endocrinol.*, 6, 549.

Levine, E. B., and Sellers, A. L. (1946) "Testosterone in Angina Pectoris", *Amer. J. med. Sci.*, 212, 7.

Lewis, R. M., and Adler, E. L. (1936) "Gonorrheal Vaginitis in Children", *Am. J. Surg.*, 3, 529.

Lisser, H., and Curtis, L. E. (1943) "Testosterone Therapy in Male Eunuchoids IV. Results from Methyl Testosterone Linguets", *J. clin Endocrinol.*, 3, 389.

Loeser, A (1937) "Resorption and Action of Follicular Hormone Rubbed into the Skin", *J. Obst. & Gynæc.*, 44, 710

Loeser, A. (1938a) "The Action of Testosterone Propionate on the Uterus and Breast", *Lancet*, 1, 373

Loeser, A. A. (1938b) "Hormone Therapy in Mastitis and Breast Cancer", *Brit. med J.*, 2, 319

Loeser, A. A. (1940) "Subcutaneous Implantation of Female and Male Hormone in Tablet Form in Women", *Brit med J.*, 1, 479.

Loeser, A A. (1941) "Mammary Carcinoma. Response to Implantation of Male Hormone and Progesterone", *Lancet*, 2, 698.

Lyon, R A (1943) "Relief of Essential Dysmenorrhea with Ethinyl Estradiol", *Surg. Gynec & Obst.*, 77, 657

Lyon, R. A. (1944) "Management of the Climacteric with Ethinyl Estradiol", *Amer J. Obstet Gynec.*, 47, 532.

MacBryde, C. M. (1939) "The Production of Breast Growth in the Human Female", *J. Amer med Ass*, 112, 1045

MacGregor, T. N (1938a) "Œstradiol Benzoate in Senile Vaginitis", *Lancet*, 2, 22.

MacGregor, T. N. (1938b) "Dysfunctional Uterine Bleeding treated with Progesterone", *Brit. med. J*, 2, 116.

Marrian, G. F. (1929) "The Chemistry of Œstrin", *Biochem J.*, 23, 1090.

Marrian, G F., and Butler, G. C (1937) "The Hormones", *Ann Rev Biochem.*, 6, 303.

Martin, P. L. (1943) "Detection of Ovulation by Basal Temperature Curve with correlating Endometrial Studies", *Amer. J. Obstet. Gynec.*, 46, 53.

Mason, H. L (1948) "Steroid Nomenclature", *J. clin Endocrinol*, 8, 190.

Mason, H. L., and Kepler, E. J. (1945) "Isolation of Steroids from Urine of Patients with Adrenal Cortical Tumors and Adrenal Cortical Hyperplasia· New 17-ketosteroid androstane-3(*a*) 11-diol-17-one", *J. biol. Chem.*, 161, 235

Masson, G (1945) "Spermatogenic Activity of Various Steroids", *Amer. J. med Sci*, 209, 324.

McCormack, G. (1946) "A Comparison of the Color Chemical Test with the Friedman Modications of the Ascheim-Zondeck Test", *Amer. J. Obstet Gynec.*, 51, 722

McCrea, L E. (1946) "Carcinoma of the Prostate: A Resumé of Treatment with Ethinyl Œstradiol, Preliminary Report", *J. Urol*, 56, 697

McCullagh, E. P. (1939) "Treatment of Testicular Deficiency with Testosterone Propionate", *J Amer. med Ass.*, 112, 1037.

McCullagh, E P., and Hruby, F. J. (1949) "Testis-Pituitary Interrelationship. The Relative Inability of Testosterone to Reduce Urinary Gonadotropin in Eunuchoid Men", *J. clin Endocrinol*, 9, 113

McCullagh, E. P, and McGurl, F. J. (1940) "Effects of Testosterone Propionate on Epiphyseal Closure, Sodium and Chloride Balance and on Sperm Counts", *Endocrinology*, 26, 377.

McEuen, C. S, Selye, H., and Collip, J. B (1936) "Some Effects of Prolonged Administration of Œstrin in Rats", *Lancet*, 1, 775.

McEuen, C S, Selye, H, and Collip, J. B (1937) "Effects of Testosterone on Somatic Growth", *Proc Soc. exp Biol. N.Y.*, 36, 307

McGinn, E J (1942) "Functional Uterine Bleeding", *J. clin. Endocrinol.*, 2, 302.

McGrath, E (1935) "Experimental Peripheral Gangrene", *J Amer. med. Ass.*, 105, 854

McGrath, E. J., and Herrmann, L. G. (1944) "Influence of Œstrogens on Peripheral Vasomotor Mechanism", *Ann. Surg.*, 120, 607

McLellan, A (1940) "Response of Non-gravid human uterus to Posterior-Pituitary Extract and its fractions Oxytocin and Vasopressin." *Lancet*, 1, 919

Meek, B E, and Murby, W H (1944) "Œstrogens for Prevention of Post-Partum Breast Engorgement", *Canad. med. Ass. J.*, 50, 241

Meyer, R K, and Hertz, R. (1937) "Effect of Œstrone on Secretion of Gonadotropic Complex as Evidenced in Parabiotic Rats", *Amer. J Physiol*, 120, 232.

Miescher, K (1944) "Ueber Steroide, Konstitution und Synthese Hochwirksame Abkömmlinge œstrogener Hormone", *Helvet chim. Acta*, 27, 1727.

Miescher, K., Scholz, C., and Tschopp, E. (1938) "The Activation of the Female Sex Hormones, I and II", *Biochem. J.*, 32, 141 and 725.

Miescher, K., and Tschopp, E. (1938) "Ueber orale Wirksamkeit männlicher Sexualhormone", *Schweiz. med. Wschr.*, 68, 1258

Miescher, K., Wettstein, A., and Tschopp, E. (1936) "The Activation of the Male Sex Hormones, I and II", *Biochem J.*, 30, 1907 and 1977.

Miller, N. E., Hubert, G., and Hamilton, J. B. (1938) "Mental and Behavioral Changes following Male Hormone Treatment of Adult Castration, Hypogonadism and Psychic Impotence", *Proc. Soc. exp. Biol N.Y.*, 38, 538.

Moir, J. C. (1934) "Recording Contractions of Human Pregnant and Non-pregnant Uterus", *Tr. Edinburgh obst. Soc*, 54, 93.

Moir, J. C. (1936) "Intrinsic Dysmenorrhoea", *Proc. R. Soc. Med*, 29, 950.

Molitch, M. (1938) "The Treatment of Acne Vulgaris with Testosterone Propionate", *Endocrinology*, 23, 803.

Moore, C. R., Lamar, J. K., and Beck, N. (1938) "Cutaneous Absorption of Sex Hormones", *J. Amer. med. Ass*, 111, 11.

Moore, C. R., and Price, D. (1937) "Some Effects of Synthetically Prepared Male Hormone (Androsterone) in the Rat", *Endocrinology*, 21, 313.

Moore, C. R, and Price, D. (1938) "Some Effects of Testosterone and Testosterone Propionate in the Rat", *Anat. Rec.*, 71, 59.

Mortimer, H., Wright, R. P., and Collip, J. B. (1936) "The Effect of the Administration of Estrogenic Hormones on the Nasal Mucosa of the Monkey (Macaca Mulatta)", *Canad. med. Ass. J.*, 35, 503, 615.

Mortimer, H, Wright, R. P., and Collip, J B. (1937) "Constitutional Factor in Atrophic Rhinitis. Treatment with Estrogenic Hormones", *Canad. med Ass J.*, 37, 445

Moseley, V. (1941) "Recurring Ulcerative Stomatitis and Vulvitis", *J. clin. Endocrinol.*, 1, 346.

Murless, B. C. (1939) "Effect of Follicular Hormone on Menopausal Flushes", *Lancet*, 1, 1205.

Nabarro, D., and Gordon Signy, A (1935) "Treatment of Vulvo-Vaginitis with Œstrin", *Lancet*, 1, 604

Nathanson, I. T., and Weisberger, D. B (1939) "The Treatment of Leukoplakia Buccalis and Related Lesions with Estrogenic Hormones", *New Engl J. Med*, 221, 556.

Nelson, W. V. (1936) "The Effect of Various Sex Hormones on the Testes of Hypophysectomised rats", *Anat Rec*, 67, 110 Suppl.

Nelson, W O. (1938) "Some Effects of Androgens and Estrogens on the Reproductive Organs and Hypophyses of Adult Male Rats", *Proc. Amer physiol. Soc*, March/April, p. 154.

Nelson, W. O., and Gallagher, T. F. (1936) "Some Effects of Androgenic Substance in Rat", *Science*, 84, 230

Nelson, W. O., and Merckel, C. (1937) "Maintenance of Spermatogenesis in Testis of the Hypophysectomised Rat with Sterol Derivatives", *Proc. Soc. exp. Biol. N.Y.*, 36, 825.

Nieburgs, H. E. (1945) "Body Temperature—Diagnostic Aid in Menstrual Disorders and Sterility", *J. Obst. & Gynæc.*, 52, 435.

Noble, R. L. (1939) "Direct Gynæcogenic and Indirect Œstrogenic Action of Testosterone Propionate in Female Rats", *J. Endocrinol.*, 1, 184.

Novak, E. (1938) "The Menopause and its Management", *J. Amer. med Ass*, 110, 619.

Papanicolaou, G. N, Ripley, H. S., and Shorr, E. (1939) "Suppressive Action of Testosterone Propionate on Menstruation and its Effect on Vaginal Smears", *Endocrinology*, 24, 339.

Parker, G. (1942) "Hæmospermia", *Proc. R. Soc. Med.*, 35, 659.

Parkes, A. S. (1936) "Increasing the Effectiveness of Testosterone", *Lancet*, 2, 674.

Parkes, A. S. (1937) "Source of Androgenic and Œstrogenic Substances in the Urine", *Lancet*, 2, 902.

Parkes, A. S (1938) "Terminology of Sex Hormones", *Nature*, 141, 36

Parkes, A S., Bishop, P. M. F., and Dodds, E. C (1936) "Œstrin and Cancer", *Lancet*, 2, 1365.

Parkes, A. S., Dodds, E. C., and Noble, R. L. (1938) "Interruption of Early Pregnancy by means of Orally Active Œstrogens", *Brit. med. J*, 2, 557.

Parkes, A. S., and Zuckerman, S. (1935) "Experimental Hyperplasia of the Prostate", *Lancet*, 1, 925.

Perlman, R. M. (1949) "Spermatogenesis following the Administration of Androgen and Gonadotropin in a case of Eunuchoidism Coincidental Neoplasm during Therapy", *J. clin. Endocrinol.*, 9, 163.

Persky, A. H., and Lipschutz, S S (1940) "Atrophic Rhinitis and its Treatment with Estrogenic Substance", *Med. Rec.*, 152, 175.

Pullen, R. L., Wilson, J. A, Hamblen, E. C., and Cuyler, W. K. (1942) "Clinical Reviews on Andrologic Endocrinology: II Treatment of Androgenic Failure", *J. clin Endocrinol*, 2, 655.

Prudente, A. (1945) "Post-operative Prophylaxis of Recurrent Mammary Cancer with Testosterone Propionate", *Surg Gynec. & Obst*, 80, 575.

Ratschow, M, and Klostermann, H C. (1938) "Experimentelle Befunde zur Gefasswirkung der Sexualhormone und ihre Beziehungen zur Klinik der peripheren Durchblutunsstörungen", *Ztschr. f klin. Med*, 135, 198

Renne, T A. C, Vest, S. A., and Howard, J E. (1939) "Clinical Studies with Male Sex Hormones III The Use of Testosterone Propionate in Impotence", *South. med J.*, 32, 1004.

Reynolds, S R. M, and Firor, W. M. (1933) "Uterine Motility in Hypophysectomised and in Pregnant Rabbits", *Amer. J. Physiol*, 104, 331

Richardson, H. B, Engle, E. T., Kurzrok, R, and Fluhmann, C F. (1941) "Functional Uterine Bleeding", *J. clin. Endocrinol*, 1, 195.

Richman, M. J, and Abarbanel, A. R. (1943) "Effect of Estradiol and Diethylstilbestrol upon the Atrophic Human Buccal Mucosa with a Preliminary Report on the Use of Estrogens in the Management of Senile Gingivitis", *J. clin. Endocrinol.*, 3, 224.

Robertson, E. M. (1937) "Study of Contractions of Non-Pregnant Human Uterus", *Edinb. med J.*, 44, 20.

Robson, J M. (1933) "Hormonic Factors Controlling Functional Activity of the Uterus", *J. Obst. & Gynæc. Brit. Emp.*, 40, 498.

Robson, J. M. (1935) "The Action of Œstrin on the Mammary Secretion", *Quart, J. exper. Physiol*, 24, 337.

Robson, J. M. (1937) "The Influence of Testosterone on Lactation", *Proc. Soc. exp. Biol. N.Y.*, 36, 153.

Robson, J. M. (1940) "Recent Advances in Sex and Reproductive Physiology", Blakiston's Son & Co, Philadelphia.

Rowlands, I. W., and Sharpey-Schafer, E. P. (1940) "Effect of Œstradiol Benzoate on the Amount of Gonadotrophin Found in the Pituitary Gland and Urine of Post-Menopausal Women", *Brit. med. J.*, 1, 205.

Rubinstein, H. S. (1938) "The Induction of Sexual Maturity in the Genitally Hypoplastic Adult through the Use of Testosterone Propionate", *J. Amer. med Ass.*, 111, 1818.

Rubinstein, H. S. (1939) "The Rationale of the Use of Testosterone Propionate in Functional Uterine Bleeding and Dysmenorrhœa", *J. lab. & clin. Med*, 24, 1026.

Rubinstein, H. S., and Abarbanel, A. R. (1939) "The Use of Testosterone Propionate in the Treatment of Dysmenorrhea", *Amer. J. Obstet. Gynec.*, 37, 709.

Rubinstein, H. S, and Kurland, A A (1939) "The Effect of Testosterone Propionate on Spermatogenesis in the Human", *South. med. J.*, 32, 499

Rubinstein, H. S., and Kurland, A A. (1941) "The Effect of Testosterone Propionate on the Rat Testis", *Endocrinology*, 28, 495.

Rusch, H. P (1937) "Reversal of Estrin-Produced Prostatic Pathology in Mice by the Use of Testosterone", *Endocrinology*, 21, 511.

Salmon, U. J. (1938a) "Skin Absorption of Dihydroxyestrin in Humans", *Proc Soc. exp. Biol. N.Y.*, 38, 481.

Salmon, U. J. (1938b) "Gonadotropic Effect of Androgens upon the Immature Rat Ovary", *Proc. Soc. exp. Biol. N.Y.*, 38, 352.

Salmon, U. J., and Geist, S H (1943) "Effect of Androgens upon Libido in Women", *J. clin Endocrinol.*, 3, 235

Salmon, U. J., Geist, S H., Gaines, J A, and Walter, R. I. (1941) "The Treatment of Abnormal Uterine Bleeding with Androgens", *Amer. J Obstet Gynec*, 41, 991.

Salmon, U J., Geist, S H., and Walter, R. I. (1939) "The Treatment of Dysmenorrhea with Testosterone Propionate", *Amer. J. Obstet. Gynec*, 38, 264

Salmon, U. J., Geist, S H, Walter, R. I., and Mintz, N. (1941) "Therapeutic Effectiveness of Orally Administered Ethinyl Estradiol", *J. clin. Endocrinol*, 1, 556

Samuels, L. T., Henschel, A F., and Keys, A. (1942) "Influence of Methyl Testosterone on Muscular Work and Creative Metabolism in Normal Young Men", *J clin. Endocrinol*, 2, 649.

Schachter, B., and Marrian, G. F. (1938) "Isolation of Estrone Sulfate from the Urine of Pregnant Mares", *J. biol. Chem*, 126, 663.

Schmitz, G. (1937) "Erfahrungen mit dem neuen synthetischen Testeshormonpräparat 'Perandren'", *Deutsche med. Wschr*, 6, 230.

Schultze, G. K. F. (1931) "Die Reaktion der nicht schwangeien Menschlichen Gebarmutter auf Hypophysenhinterlappenextrakte", *Zbl. f. Gynak.*, 55, 3042.

Schultz, F. W., and Anderson, C. E. (1943) "Endocrine Treatment of Enuresis", *J. clin. Endocrinol.*, 3, 405.

Schwander, H., and Marvin, H. N. (1947) "Treatment of Carcinoma of the Human Breast with Testosterone Propionate: A Report of Five Cases", *J. clin. Endocrinol.*, 7, 423.

Scowen, E. F. (1944) "The Metabolism and Therapeutic Use of Progesterone", *Proc. R. Soc. Med*, 37, 677.

Segaloff, A. (1944) "The Intrasplenic injection of some Synthetic Œstrogens and Proestogens", *Endocrinology*, 34, 335.

Segaloff, A. (1949) "Ethinyl Estradiol", *J clin. Endocrinol*, 9, 573.

Selye, H., Collip, J. B, and Thomson, D. L. (1935) "Effect of Estrin on Ovaries and Adrenals", *Proc. Soc. exp Biol. N.Y.*, 32, 1377.

Selye, H, and Friedman, S. (1941) "The Action of Various Steroid Hormones on the Testis", *Endocrinology*, 28, 129

Severinghaus, E. L. (1944) "Therapy of the Patient in the Menopause Endocrine Methods", *J. clin. Endocrinol.*, 4, 597.

Shapiro, H. (1937) "Effects of Testosterone Propionate on Mating", *Nature*, 139, 588.

Sharpey-Schafer, E. P., and Shackman, R. (1939) "Testosterone Propionate—Its Effect on the Histology of Prostatic Enlargement in Man", *Lancet*, 1, 1254

Shay, H., Gershon-Cohen, J, Paschkis, K. E, and Fels, S. S. (1941) "Inhibition and Stimulation of Testes in Rats Treated with Testosterone Propionate", *Endocrinology*, 28, 485.

Shelesnyak, M. C., and Rosen, S (1938) "Naso-Genital Relationship" *Endocrinology*, 23, 58.

Shelton, E K., Varden, A E, and Mark, J. S. (1947) "Experimental Use of Testosterone Compounds in Premature Infants", *J clin Endocrinol.*, 7, 708.

Shimkin, M B, Lorenz, E., Wyman, R, and Norton, S. G. (1944) "Absorption of Subcutaneously Implanted Hormone Pellets", *Endocrinology*, 35, 283.

Siegler, S L, and Silverstein, L M (1940) "The Use of Testosterone Propionate in the Inhibition of Lactation during the Puerperium", *Amer J. Obstet Gynec*, 39, 109

Simonson, E, Kearns, W M, and Enzer, N (1944) "Effect of Methyl Testosterone Treatment on Muscular Performance and the Central Nervous System of Older Men", *J clin Endocrinol*, 4, 528.

Simpson, M E, and Evans, H M. (1946) "Comparison of the Spermatogenic and Androgenic Properties of Testosterone Propionate with Those of Pituitary ISCH in Hypophysectomized 40-Day-Old Male Rats", *Endocrinology*, 39, 281.

Simpson, S. L. (1948) "Discussion on Simmonds's Disease", *Proc. R. Soc. Med.*, 41, 192.

Simpson, S. L., de Fremery, P., and Macbeth, A. (1936) "Presence of Excess of 'Male' (Comb Growth and Prostate Stimulating) Hormone in Virilism and Pseudo-Hermaphroditism", *Endocrinology*, 20, 363.

Smith, A van S., Smith, O. W, and Pincus, G. (1938) "Total Urinary Estrogen, Estrone and Estriol during a Menstrual Cycle and Pregnancy", *Amer. J. Physiol*, 121, 98.

Sollenberger, R. T, and Hamilton, J. B. (1939) "The Effect of Testosterone Propionate upon the Sexual Behaviour of Castrated Male Guinea Pigs", *J. comp. Psychol*, 28, 81.

Soule, S. D. (1941) "Anhydro-hydroxy-progesterone in Dysmenorrhea", *J. clin. Endocrinol*, 1, 567.

Soule, S. D. (1942) "Estrogen withdrawal Bleeding. A Study of Comparative Activity of Various Estrogens", *Amer. J. Obstet. Gynec*, 44, 684.

Soule, S D. (1943) "A Clinical Trial of Ethinyl Estradiol", *Amer. J. Obstet Gynec.*, 45, 315.

Spence, A. W. (1939a) "Testosterone Propionate in Chronic Mastitis", *St. Bart's Hosp. Rep.*, 72, 75

Spence, A W. (1939b) "Testosterone Propionate in Chronic Mastitis", *Lancet*, 2, 820.

Spence, A. W. (1940a) "Preparations of Testosterone in Eunuchism and Hypogonadism", *Quart. J. Med.*, 9, 309.

Spence, A. W. (1940b) "Testosterone Propionate in Functional Impotence", *Brit. med J*, 2, 411.

Spence, A. W. (1940c) "Local Inunction of Testosterone in Chronic Mastitis", *Lancet*, 2, 387

Spence, A. W (1942) "Sublingual Administration of Methyl Testosterone", *Brit med J*, 1, 668.

Spurrel, W. R, and Ucko, H (1938) "Studies in Clinical Endocrinology", *Guy's Hosp. Rep.*, 2, 230.

Starkey, W. F., and Leathem, J. H. (1938) "Gonadotropic Action of Testosterone Propionate on Immature Mouse Ovary", *Proc. Soc. exp. Biol N.Y.*, 39, 218.

Steinach, E., and Kun, H. (1937) "Transformation of Male Sex Hormones into a Substance with the Action of a Female Hormone", *Lancet*, 2, 845.

Sturgis, S. H., and Albright, F. (1940) "The Mechanism of Estrin Therapy in the Relief of Dysmenorrhea", *Endocrinology*, 26, 68.

Suzman, M. M, Freed, C. C., and Prag, J J (1938) "Studies on Experimental Peripheral Vascular Disease with special Reference to Thrombo-angiitis obliterans", *S Afr. J. med Sci*, 3, 29

Taylor, S. G, Slaughter, D., and Preston, F. W. (1948) "Treatment of Far-advanced Inoperable Carcinoma of the Breast with Estrogens and Androgens", *J. clin Endocrinol*, 8, 585.

Tebbut, H. K. (1938) "Male Hormone. Effect upon the Nasal Mucosa of Man and Monkey", *N.Y S. J. Med.*, 38, 5, 332.

Te Linde, R. W. (1938) "The Treatment of Gonococcic Vaginitis with the Estrogenic Hormone", *J. Amer. med. Ass*, 20, 1633.

Thomas, H. B, and Hill, R. T. (1940) "Testosterone Propionate and the Male Climacteric", *Endocrinology*, 26, 953.

Thorn, G. W., and Harrop, G A. (1937) "The 'Sodium Retaining Effect' of the Sex Hormones", *Science*, 86, 40.

Törnblom, N. (1942) "Internal Secretion of the Germinal Tissue of the Testes and Prostatic Hypertrophy", Almqvist & Wiksells, Upsala.

Tscherne, E. (1939) "Zur Beeinflussung des Haarwachtstums durch Follikelhormon", *Dsch. med. Wschr.*, 65, 1692.

Turner, H. H. (1939) "The Clinical Use of Synthetic Male Sex Hormone", *Endocrinology*, 24, 763

Turpault, M. (1937) "Que peut-on obtenir avec le Propionate de Testostérone ?", *C.R. Soc. Trans Gynecol.*, 7, 6, 181.

Ucko, H. (1946) "Persistent Enuresis", *Lancet*, 2, 400

Vaux, N. W., and Rakoff, A. E (1945) "Treatment of Habitual Abortion with Estrogen and Progesterone", *Surg. Clin N. Amer.*, 25, 1324.

Venning, E. H, and Browne, J. S. L (1936) "Isolation of a Water-Soluble Pregnandiol Complex from Human Pregnancy Urine", *Proc. Soc. exp. Biol. N Y.*, 34, 792.

Venning, E H., and Browne, J S. L (1937) "Studies on Corpus Luteum Function", *Endocrinology*, 21, 711.

Vest, S. A, and Howard, J. E. (1938) "Clinical Experiments with the use of Male Sex Hormones", *J. Urol*, 1, 155

Villaret, M., Justin-Besancon, L., and Rubens-Duval, S. (1938) "Remarques sur les Effets due Propionate de Testostérone dans a case D'Eunuchoidisme Post-Pubère", *C.R Soc. Biol. Paris*, 127, 7, 599.

Venzmer, G. (1937) "Behandlung sexueller Störungen mit synthetischem Mannhormon", *Med Welt*, 11, 752.

Waldman, S. (1945) "The Treatment of Angina Pectoris with Testosterone Propionate", *J clin Endocrinol*, 5, 305.

Walker, K. (1937) "Hormone Deficiencies in the Male", *Brit med. J.*, 1, 623.

Walker, T. C. (1942) "Use of Testosterone Propionate and Estrogenic Substance in Treatment of Essential Hypertension, Angina Pectoris, and Peripheral Vascular Disease", *J clin Endocrinol.*, 2, 560.

Walsh, E. L, Cuyler, W. K., and McCullagh, D R. (1934) "The Physiological Maintenance of the Male Sex Glands. The Effect of Androstin on Hypophysectomised Rats", *Amer. J. Physiol*, 107, 508

Walton, R P. (1944) "Sublingual Administration of Drugs", *J. Amer med Ass.*, 124, 138

Warwick, M. H., and Parkes, A S (1940) "Absorption of Progesterone and Desoxycorticosterone", *Lancet*, 1, 406.

Watkinson, G, McMenemey, W. H, and Evans, G. (1947) "Hypopituitarism Hypogonadism and Anaemia Treated with Testosterone", *Lancet*, 1, 631.

Watson, B. A. (1942) "Clinical Experiences with Oral Ethinyl Estradiol", *J. clin. Endocrinol.*, 2, 447.

Webster, B. (1938) "The Treatment of Hypogonadism in the Adolescent Male", *J. Pediat.*, 13, 847.

Wells, L. J (1943) "Effects of Large Doses of Androgen on the Testis in the Ground Squirrel (Citellus Tridecemlineatus)", *Endocrinology*, 32, 455.

Wells, L. J., and Moore, C R. (1936) "Hormonal Stimulation of Spermatogenesis in the Testis of the Ground Squirrel", *Anat. Rec.*, 66, 181.

Werner, A. A. (1939) "The Male Climacteric", *J. Amer. med. Ass*, 112, 1441.

Werner, S C., and West, R. (1943) "Nitrogen Retention, Creatinuria, and other Effects of Treatment of Simmonds's Disease with Methyl Testosterone", *J. clin. Invest.*, 22, 335.

White, J. C, and Smithwick, R. (1942) "Automatic Nervous System", 2nd Edit., London

Whitney, R., and Burdick, H O. (1936) "Tube-Locking of Ova by Œstrogenic Substances", *Endocrinology*, 20, 643.

Wiesbader, H., and Filler, W. (1946) "Oral Therapy with Ethinyl Estradiol in the Menopause", *Amer. J. Obstet. Gynec.*, 51, 75.

Williams, G., and Nomland, R. (1937) "Gonadotropic Substance in the Treatment of Acne", *J. Amer. med. Ass.*, 109, 564.

Williams, W. W. (1943) "Basal Metabolic Rate, Basal Body Temperatures and Ovarian Cycle", *Amer. J. Obstet. Gynec.*, 46, 662.

Williams, R H., Whittenberger, J. L., Bissell, G W., and Weinglass, A. P. (1945) "Treatment of Adrenal Insufficiency", *J. clin. Endocrinol.*, 5, 163.

Wilson, L., and Kurzrok, R (1938) "Studies on Motility of Human Uterus in Vivo· Functional Myometrial Cycle", *Endocrinology*, 23, 79.

Wolfe, J. M., and Chadwick, C. S (1936) "Quantitative Studies on the Structural Changes Induced in the Anterior Hypophysis by Injections of Estrin", *Endocrinology*, 20, 503.

Wolfe, J. M., and Hamilton, J. B. (1937) "Comparative Action of Testosterone Compounds, of Estrone and of Combinations of Testosterone Compounds and Estrone on the Anterior Hypophysis", *Endocrinology*, 21, 603.

Wright, R. P., and Collip, J. B. (1936) "Effect of Estrogenic Hormones on Nasal Mucosa", *Canad med. Ass. J.*, 35, 615

Zehn, P. (1939) "Die Enuresis und Ihre Behandlung mit Männlichem Sexualhormon", *Dtch med. Wschr*, 65, 1831.

Ziserman, A. J. (1935) "Ulcerative Vulvitis and Stomatitis of Endocrine Origin", *J. Amer med. Ass*, 104, 825

[illegible]

Zondek, B. (1936b) "Tumour of the Pituitary Induced with Follicular Hormone", *Lancet*, 1, 776.

Zondek, B. (1936c) "Impairment of Anterior Pituitary Functions by Follicular Hormone", *Lancet*, 2, 842.

Zondek, B. (1942) "Simplified Hormonal Treatment of Amenorrhoea", *J. Amer. med. Ass*, 118, 705.

Zondek, B., Rozin, S., and Vesell, M. (1940) "Uterine Bleeding Induced by Progesterone during Normal Menstrual Interval and in Amenorrhoea", *Amer. J. Obstet Gynec.*, 40, 391.

Zuckerman, S. (1936) "Inhibitory Effect of Testosterone Propionate on Experimental Prostatic Enlargement", *Lancet*, 2, 1259

Zuckerman, S (1937) "Inhibition of Menstruation and Ovulation by means of Testosterone Propionate", *Lancet*, 2, 676.

Zuckerman, S. (1938) "The Effect of Testosterone Propionate on Testicular Function in Monkeys", *Lancet*, 1, 1162.

Zuckerman, S., and Parkes, A. S. (1936) "Effect of Sex Hormones on the Prostate of Monkeys", *Lancet*, 1, 242.

Zuckerman, S., and Sandys, O. C. (1939) "Further Observations on the Prostate and Seminal Vesicles of Monkeys", *J. Anat.*, 73, 597.

Zurrow, H., Soland, G., Klein, C., and Goldman, S. (1942) "The Effect of Testosterone Propionate in the Treatment of Arteriosclerosis Obliterans", *J. lab. & clin. Med.*, 28, 269.

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INDEX

INDEX

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